초보 호흡기학 연구자를 위한 빅데이터 리서치

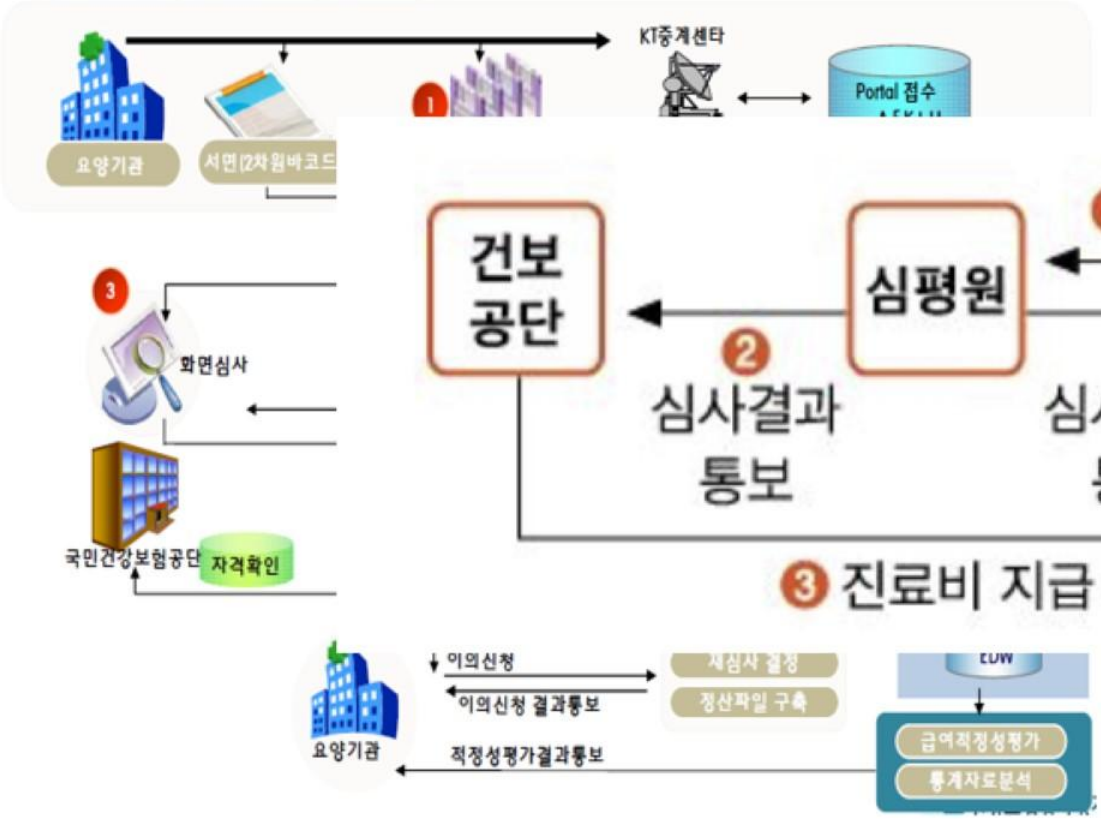
Danbee Kang, PhD
Center for Clinical Epidemiology, SMC
Department of Clinical Research Design & Evaluation, SAIHST, SKKU

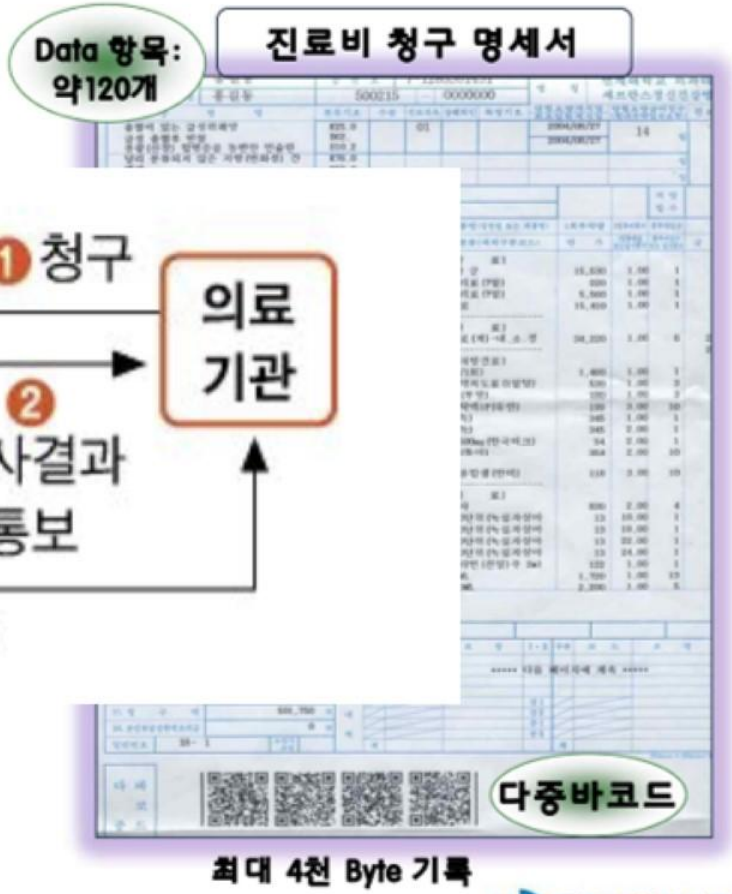
1 . 자료원소개

1. 청구데이터의 이해

1 청구데이터의 이해

청구자료 처리 흐름도





최대 4천 Byte 기록

1 청구데이터의 이해

- 보험급여가 인정된 의료이용만 포함됨 (EX. 비 급여 진료, 처방 없이 약 구입, 미용 등)
- 수가 코드로 정의 내리기 어려운 경우 (실제 임상현장에서 잘 넣지 않는 코드 등) 연구 불가
  (EX. 지방간 -> 단 코드 대신 검진자료 활용하여 fatty liver index 등으로)
- 수치자료 등 없음 (검사의 여부는 알 수 있으나 검사의 결과는 알 수 없음).
  단, 검진자료만 가능함!
- 청구자료를 기준으로 하기 때문에 동일 청구서에서의 순서 확인 어려움
  (EX. 동일 입원 내에서는 선 후 관계 알 수 없음)

1 청구데이터의 이해

- ○ 대표성 – 전국민을 대표하는 자료로서 일반화 용이
- ○ 자료의 완결성
  - 동일한 사람에 대해 장기간 관찰 가능
  - 추적관찰 실패가 거의 없음
- ○ Real world data
  - 행위 별 수가제 하의 청구자료 구축으로 세부 의료이용 내역 확인가능
  - 제한적 실험적 환경이 아닌 실제 의료행위에 대한 현황 분석가능 (약제 사용 패턴, 용량조절 등)
- ○ 대규모 데이터 사이즈: 큰 통계적 파워, 작은 오차범위, 다양한 보정변수
  - 드물게 발생하는 사건 (희귀질병, 합병증, 약물 부작용, 희소하게 사용되는 진료행위)에 대한 연구
- ○ 이미 구축된 데이터를 활용하므로 비용 및 시간 절약

1 청구데이터의 이해

구분	건강보험자료 (공단, 심평원)	병원 EMR자료	Registry 자료 (전향적 코호트)
자료 특성	기구축된 청구자료로 후향적 연구 수행	병원의 의무기록 자료로 후향적 연구 수행	연구대상을 직접 모집하여 추적 관찰
자료의 규모	5천만명 전국민의 인구학적 정보 및 의료 이용기록 포괄	단일 병원 자료로 내원 환자만을 대상으로 함	Registry 규모에 따라 다르며, 다기관 연구의 경우, 충분한 연구대상수 확보 가능
자료의 충실도	급여 청구에 필요한 정보의 충실도는 높으나 건강검진자료의 충실도는 낮음	내원 환자의 의료이용기록으로 상대적으로 자료의 충실도가 높음	2-3년에 한 번씩 정보를 수집할 경우, 추적관찰 시점 사이의 정보가 누락됨.
자료의 접근성	분석용 원격 대형 서버 활용 및 지역 분석 센터 배정으로 자료에 대한 접근성 높음	기 구축되어 있는 분석 인프라 활용 가능 대상자 비식별화 이슈 존재	Registry 구성에 참여한 기관 동의 및 공통데이터모델을 통한 변환 필요
장점	• 기구축된 후향적 자료 활용으로 비용 절감 가능 • 장기간 추적관찰 가능 • 전체 인구집단을 대상으로 하여 외적 타당도가 높은 연구 수행 가능	• 랩수치, 병기 등 임상정보 확보 가능. • 진단명의 타당도가 높음. • 비급여 의료이용 기록 확인가능	• 결과변수의 타당도가 높음. • 연구목적에 맞는 대상자 선별이 가능하며, 보다 정확하게 환자특성 파악 가능함
단점	• 이상사례 증상 정보 확인 불가능 • 랩수치 등 임상정보 부족 • 비급여 기록 확인 불가	• 단일병원 자료로 희귀질환연구에서 검정력 확보 어려움 • 연구결과 일반화 어려움	• Registry 구축에 고비용이 소요됨 • 회상 비뚤림(recall bias)의 영향을 받을 수 있음

2. 청구데이터 활용

2 청구데이터의 활용 – 현황 파악

Hwang et al. Ann. Intensive Care (2019) 9:65
https://doi.org/10.1186/s13613-019-0534-7

Annals of Intensive Care

RESEARCH Open Access

Changes in acute kidney injury epidemiology in critically ill patients: a population-based cohort study in Korea

Subin Hwang[1†], Hyejeong Park[2†], Youngha Kim[2], Danbee Kang[2,3], Ho Suk Ku[1], Juhee Cho[2,3], Jung Eun Lee[4], Wooseong Huh[4], Eliseo Guallar[2,5], Gee Young Suh[2,6*] and Hye Ryoun Jang[4*]

Abstract

Background: Although no specific treatment facilitates renal tubular regeneration in acute kidney injury (AKI), the rapid increase in aging populations with more comorbidities and advances in critical care management are expected to change the epidemiology of AKI. However, few recent studies dissected the current epidemiologic characteristics of critically ill patients with AKI. We investigated recent epidemiologic changes in severe AKI in critically ill patients.

Methods: All adult admissions to intensive care units (ICUs) in Korea from 2008 to 2015 were screened using the national health insurance review and assessment database, and 1,744,235 patients were included. Clinical characteristics and changes in AKI incidence and mortality rate were analyzed.

Results: The incidence of AKI increased from 7.4% in 2008 to 8.3% in 2015 (p for trend < 0.001). Age-standardized AKI rate was 7018.6 per 100,000 person-years. In-hospital mortality significantly decreased from 39.1% in 2008 to 37.2% in 2015 (p for trend < 0.001) with 2427.6 deaths per 100,000 person-years. Patients with AKI showed higher in-hospital mortality, prolonged ICU length of stay, and higher total cost. Multivariable analysis showed increased risk of in-hospital mortality (adjusted odds ratio [OR] 3.74), mechanical ventilation (OR 2.87), ECMO (OR 6.99), and vasopressor requirement (OR 2.75) in patients with AKI.

Conclusions: Recent advances in medical management for AKI have improved in-hospital mortality of critically ill patients with AKI despite increases in the elderly population and AKI incidence.

Keywords: Acute kidney injury, Critically ill patients, Intensive care unit, Mortality

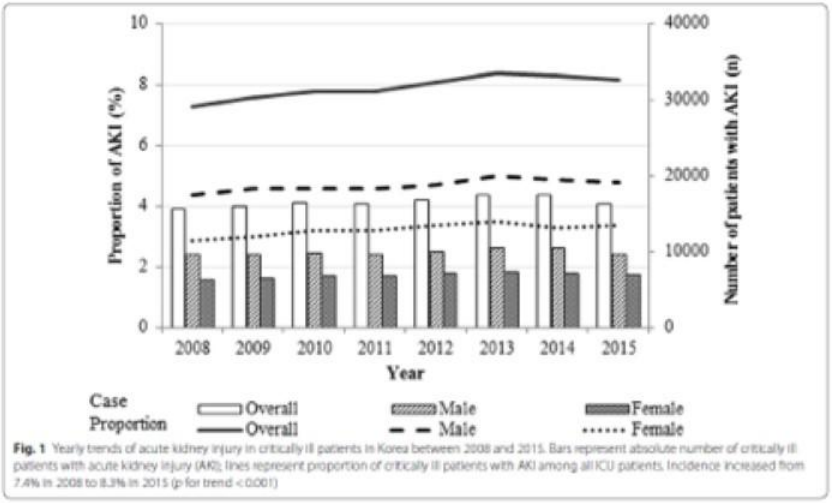


Fig. 1 Yearly trends of acute kidney injury in critically ill patients in Korea between 2008 and 2015. Bars represent absolute number of critically ill patients with acute kidney injury (AKI); lines represent proportion of critically ill patients with AKI among all ICU patients. Incidence increased from 7.4% in 2008 to 8.3% in 2015 (p for trend < 0.001)

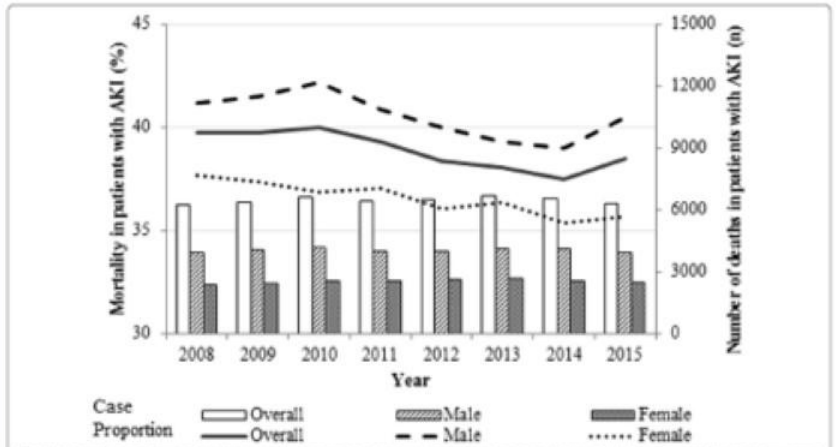


Fig. 2 In-hospital mortality rate in critically ill patients with acute kidney injury in Korea between 2008 and 2015. Bars represent absolute number of deaths in critically ill patients with acute kidney injury (AKI); lines represent mortality of critically ill patients with AKI. Mortality decreased from 39.1 to 37.2% (p for trend < 0.001)

2 청구데이터의 활용 – 현황 파악

ESC European Society of Cardiology

European Journal of Heart Failure (2024) 26, 1594–1603
doi:10.1002/ejhf.3333

RESEARCH ARTICLE

In-hospital and long-term outcomes of cardiogenic shock complicating myocardial infarction versus heart failure

Ki Hong Choi[1†], Danbee Kang[2,3†], Hyejeong Park[3], Taek Kyu Park[1], Joo Myung Lee[1], Young Bin Song[1], Joo-Yong Hahn[1], Seung-Hyuk Choi[1], Hyeon-Cheol Gwon[1], Juhee Cho[2,3]*, and Jeong Hoon Yang[1,4]*

[1]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, Republic of Korea; [3]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; and [4]Department of Critical Care Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

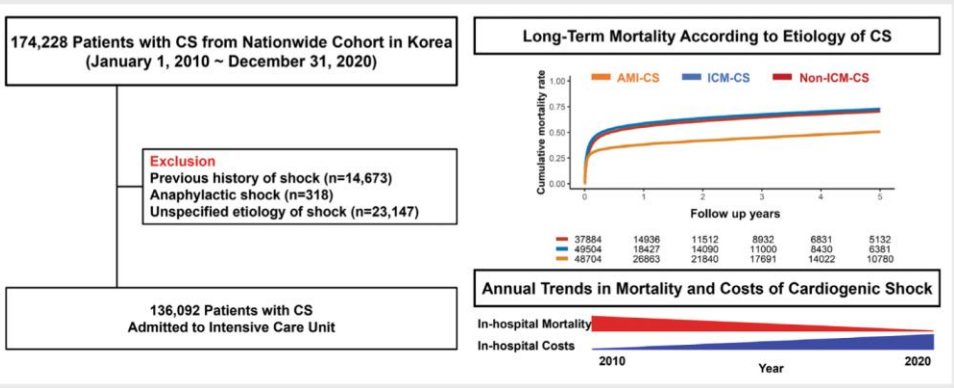
Received 27 February 2024; revised 20 May 2024; accepted 21 May 2024; online publish-ahead-of-print 10 June 2024

Aims This study sought to examine the difference in clinical characteristics, treatment strategy, trends in mortality, and medical costs according to the aetiologies of cardiogenic shock (CS).

Methods and results This was a population-based, nationwide, cohort study from the Korean National Health Insurance Service database. All CS adults (≥18 years) were admitted to an intensive care unit from January 2010 to December 2020. The primary outcome was in-hospital mortality. The secondary outcomes were cardiac replacement therapy (left ventricular assisted device implantation or heart transplantation), all-cause mortality, ischaemic stroke, rehospitalization for heart failure (HF) during follow-up, and actual in-hospital medical costs. Among 136 092 individuals with CS, 48 704 (29.7%) cases were due to acute myocardial infarction-related CS (AMI-CS), and the remaining 87 388 (71.3%) were due to HF-CS (ischaemic cardiomyopathy [ICM] vs. non-ICM, 49 504 [56.6%] vs. 37 884 [45.4%]). Patients with HF-CS were older, less likely to be male, and less likely to receive mechanical circulatory support, compared to those with AMI-CS. During the 10-year study period, the in-hospital mortality rate decreased, and actual medical costs tended to increase, regardless of CS aetiology. Compared with AMI-CS, HF-CS was associated with higher risks of in-hospital mortality (40.3% vs. 28.5%; adjusted odds ratio [OR] 1.47, 95% confidence interval [CI] 1.43–1.52), cardiac replacement therapy (adjusted OR 1.65, 95% CI 1.16–2.34), as well as follow-up mortality after successful discharge (19.3% vs. 8.5%; adjusted-hazard ratio 1.54, 95% CI 1.48–1.59). HF-CS had lower medical costs than AMI-CS (adjusted ratio 0.79, 95% CI 0.79–0.80).

Conclusions With medical advances during the past 10 years, the mortality of CS has decreased significantly, but the mortality of HF-CS remains high. The findings highlight the need for effective treatment strategies for patients with HF-CS.

[†]Contributed equally as first co-authors.



2 청구데이터의 활용 – 질환이 다른 질환의 위험인자 인지 ? (추적관찰이 모두 가능함)

JAMA Oncology | Original Investigation

Incidence of Diabetes After Cancer Development
A Korean National Cohort Study

Yul Hwangbo, MD, MSc; Danbee Kang, PhD; Minwoong Kang, MSc; Saemina Kim, MSc; Eun Kyung Lee, MD, PhD; Young Ae Kim, PhD; Yoon Jung Chang, MD, PhD; Kui Son Choi, PhD; So-Youn Jung, MD, PhD; Sang Myung Woo, MD, MSc; Jin Seok Ahn, MD, PhD; Sung Hoon Sim, MD, PhD; Yun Soo Hong, MD, MHS; Roberto Pastor-Barriuso, PhD; Eliseo Guallar, MD, DrPH; Eun Sook Lee, MD, PhD; Sun-Young Kong, MD, PhD; Juhee Cho, PhD

Key Points

Question Does cancer increase the risk of diabetes?

Findings In a Korean general population cohort of 524 089 men and women observed for up to 10 years, participants who developed cancer had a clear increase in the subsequent risk of diabetes, even after taking into account precancer risk factors.

Meaning Physicians should remember that patients with cancer develop other clinical problems, such as diabetes, with higher frequency than individuals without cancer, and should consider routine diabetes screening in these patients.

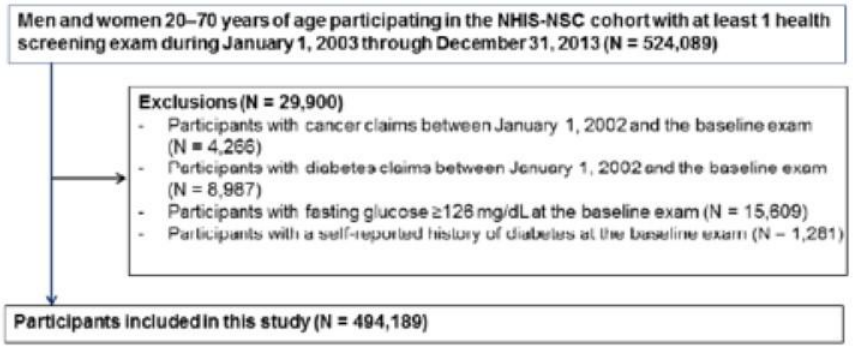
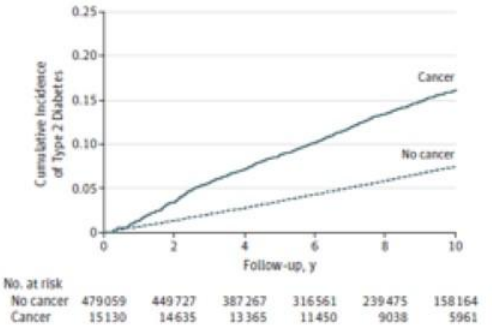


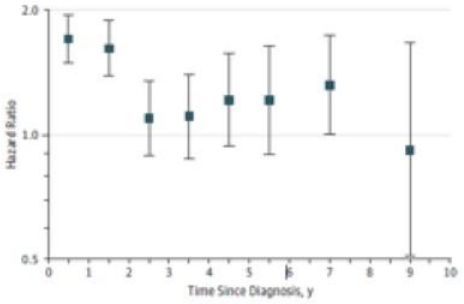
Figure 1. Cumulative Incidence of Diabetes by Cancer Status



No. at risk						
No cancer	479059	449727	387267	316561	239475	158164
Cancer	15130	14635	13365	11450	9038	5961

Cumulative incidence was calculated using Kaplan-Meier curves. Participants who developed cancer contributed person-time to the exposed group from the time of cancer development. Unexposed person-time was contributed by participants who did not develop cancer and by participants who developed cancer prior to diabetes development. To reduce the potential impact of surveillance bias, we excluded from the analysis cases of diabetes that occurred in the first 31 days after cancer diagnosis (n = 72).

Figure 2. Hazard Ratios for Incident Diabetes Associated With Cancer Development by Time Since Cancer Diagnosis



Adjusted for age (20-29, 30-39, 40-49, 50-59, and 60-69 years) and sex. Model 2 was further adjusted for body mass index (continuous), smoking (never, former, current, and missing), and frequency of alcohol intake (<1 time per month, 1-2 times per week, 3-4 per week, almost every day, and missing). Model 3 was further adjusted for hypertension (yes or no), hyperlipidemia (yes or no), Charlson comorbidity index (0, 1, 2, ≥3), systolic blood pressure (continuous), fasting glucose (continuous), and total cholesterol (continuous). Error bars indicate 95% confidence intervals.

2 청구데이터의 활용 – 질환이 다른 질환의 인자인지 (발생률이 작은것도 가능함)

Blood Cancer Journal www.nature.com/bcj

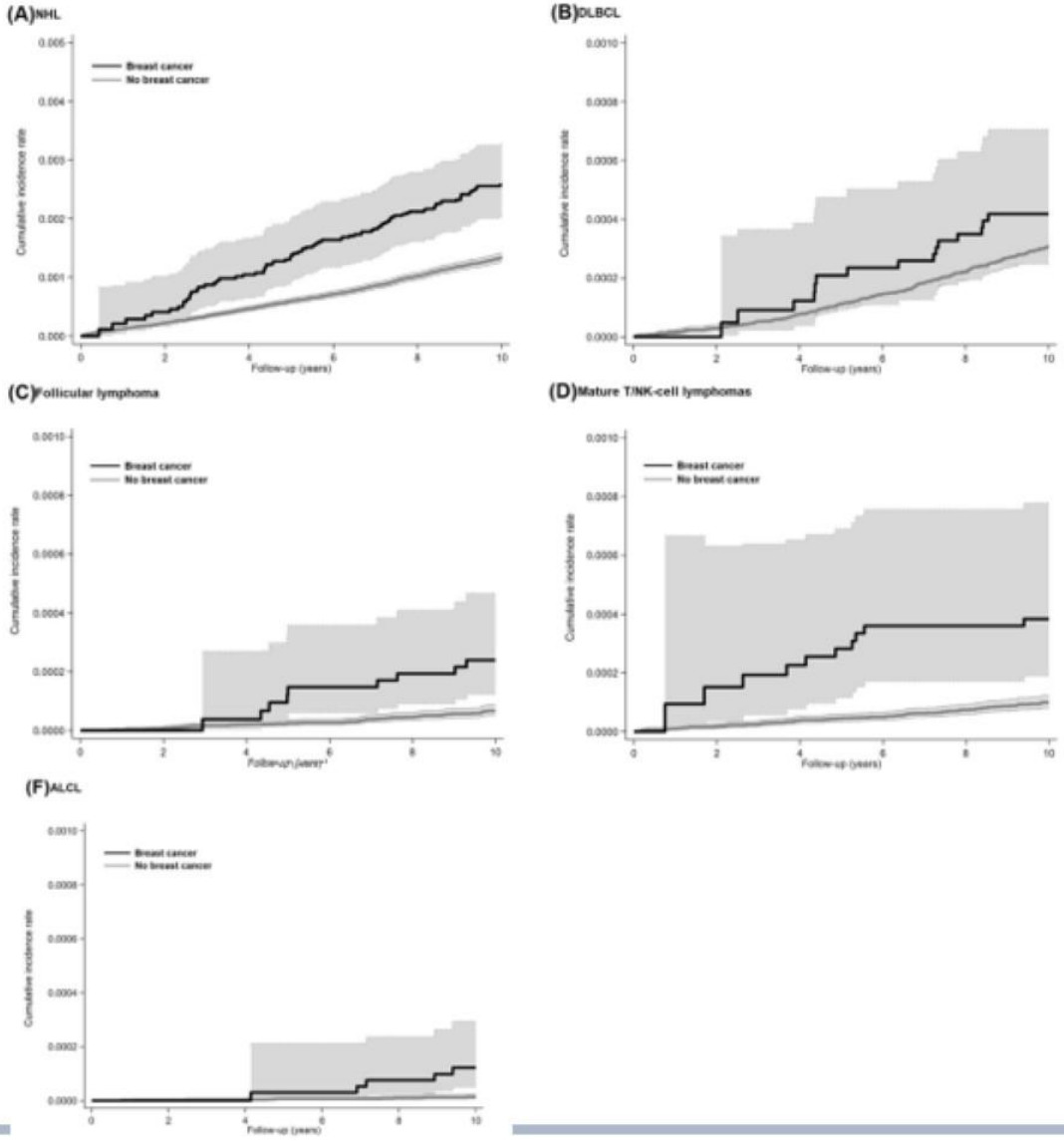
ARTICLE OPEN

Risk of non-Hodgkin lymphoma in breast cancer survivors: a nationwide cohort study

Danbee Kang[1,2,9], Sang Eun Yoon[3,9], Dongwook Shin[1,4], Jin Lee[1,2], Yun Soo Hong[5], Se Kyung Lee[6], Jeong Eon Lee[6], Yeon Hee Park[3], Jin Seok Ahn[3], Eliseo Guallar[2,3], Won Seog Kim[3,7], Jungho Lee[8], Seok Jin Kim[3,7]✉ and Juhee Cho[1,2,3]✉

Several studies have suggested that estrogens have a protective function against lymphomagenesis. The treatment of breast cancer is driven by subtype classification, and the assessment of hormone receptor status is important for treatment selection. Thus, we evaluated the association between breast cancer and the incidence of NHL. We conducted a retrospective cohort study using a population-based nationwide registry in South Korea. We selected all women with newly diagnosed breast cancer between January 1st, 2002 and December 31st, 2016 who received curative treatment ($N = 84,969$) and a 1:10 sample of age-matched non-breast cancer controls ($N = 1,057,674$). Incident breast cancer (time-varying exposure) was the exposure and development of any type of NHL, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mature T/NK-cell lymphomas, anaplastic large cell lymphoma (ALCL), and unspecified types of NHL, was the outcome. During follow-up, 1564 incident cases of NHL occurred. The fully adjusted Hazard Ratio (HR) for NHL associated with the development of breast cancer was 1.64 (95% CI = 1.34–2.00) after adjusting for body mass index, alcohol intake, physical activity, smoking, income, and comorbidity. The adjusted HR for NHL was much higher in participants who were aged <50 years and who received hormone therapy (either tamoxifen or aromatase inhibitors) than in those ≥50 years or who did not receive hormone therapy, respectively. The development of breast cancer was associated with a significantly increased risk of NHL, particularly follicular lymphoma and mature T/NK-cell lymphoma. In particular, the risk of NHL was higher in patients receiving hormone therapy and in younger patients.

Blood Cancer Journal (2021)11:200 ; https://doi.org/10.1038/s41408-021-00595-0



2 청구데이터의 활용 – RCT 검증

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 5, 2023
© 2023 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

Combination Lipid-Lowering Therapy in Patients Undergoing Percutaneous Coronary Intervention

Seung-Jun Lee, MD,[a,*] Jae Hong Joo, PhD,[b,c,*] Sohee Park, PhD,[c] Choongki Kim, MD,[d] Dong-Woo Choi, PhD,[e] Sung-Jin Hong, MD,[a] Chul-Min Ahn, MD,[a] Jung-Sun Kim, MD,[a] Byeong-Keuk Kim, MD,[a] Young-Guk Ko, MD,[a] Donghoon Choi, MD,[a] Yangsoo Jang, MD,[f] Chung-Mo Nam, PhD,[b] Myeong-Ki Hong, MD[a]

ABSTRACT

BACKGROUND The RACING (randomized comparison of efficacy and safety of lipid-lowering with statin monotherapy versus statin/ezetimibe combination for high-risk cardiovascular diseases) trial examined the effects of combination therapy with moderate-intensity statin and ezetimibe in patients with atherosclerotic cardiovascular disease compared with high-intensity statin monotherapy.

OBJECTIVES This observational study was conducted to evaluate the impact of 2 treatment strategies used in the RACING trial in clinical practice.

METHODS After stabilized inverse probability of treatment weighting, a total of 72,050 patients who were prescribed rosuvastatin after drug-eluting stent implantation were identified from a nationwide cohort database: 10,794 patients with rosuvastatin 10 mg plus ezetimibe 10 mg (combination lipid-lowering therapy) and 61,256 patients with rosuvastatin 20 mg monotherapy. The primary endpoint was the 3-year composite event of cardiovascular death, myocardial infarction, coronary artery revascularization, hospitalization for heart failure treatment, or nonfatal stroke in accordance with the RACING trial.

RESULTS Combination lipid-lowering therapy was associated with a lower occurrence of the primary endpoint (11.6% vs 15.2% for those with high-intensity statin monotherapy; HR: 0.75; 95% CI: 0.70-0.79; $P < 0.001$). Compared with high-intensity statin monotherapy, combination lipid-lowering therapy was associated with fewer discontinuations of statin (6.5% vs 7.6%; HR: 0.85; 95% CI: 0.78-0.94: $P < 0.001$) and a lower occurrence of new-onset diabetes requiring medication (7.7% vs 9.6%; HR: 0.80; 95% CI: 0.72-0.88; $P < 0.001$).

CONCLUSIONS In clinical practice, combination lipid-lowering therapy with ezetimibe and moderate-intensity statin was associated with favorable clinical outcomes and drug compliance in patients treated with drug-eluting stent implantation. (CONNECT DES Registry; NCT04715594) (J Am Coll Cardiol 2023;82:401-410) © 2023 by the American College of Cardiology Foundation.

Recently, the RACING (randomized comparison of efficacy and safety of lipid-lowering with statin monotherapy versus statin/ezetimibe combination for high-risk cardiovascular diseases) trial demonstrated the noninferiority of combination lipid-lowering therapy with moderate-intensity statin and ezetimibe compared with high-intensity statin monotherapy regarding 3-year adverse cardiovascular outcomes in patients with ASCVD.[8] Combination lipid-lowering therapy was correlated with increased drug adherence and greater LDL-C reduction than high-intensity statin monotherapy.[8]

The purpose of the present study was to assess the general applicability of the RACING trial results in patients who underwent PCI in a clinical setting. Using the Korean nationwide cohort database, we assessed the association between combination lipid-lowering therapy and the occurrence of the clinical endpoints of the RACING trial in comparison with high-intensity statin monotherapy.

Supplemental Table 1. Summary of strategies for emulating RACING trial

Components	RACING trial	This study
Inclusion period	14 Feb 2017 – 18 Dec 2018	1 Jan 2016 – 31 Dec 2018
Eligibility criteria	Adults (19 – 80 years) with documented ASCVD (previous myocardial infarction, acute coronary syndrome, coronary revascularization or other arterial revascularization, ischemic stroke, or peripheral artery disease)	Adults (≥20 years of age) who underwent DES implantation between 2005 and 2016.
Exposed group	Combination lipid-lowering therapy: Rosuvastatin 10 mg with ezetimibe 10 mg daily	Combination lipid-lowering therapy: Rosuvastatin 10 mg with ezetimibe 10 mg daily
Unexposed group	High-intensity statin monotherapy: Rosuvastatin 20 mg daily	High-intensity statin monotherapy: Rosuvastatin 20 mg daily
Primary endpoint	3-year composite of cardiovascular death, coronary or peripheral revascularization, hospitalization for cardiovascular events, or non-fatal stroke within 3 years.	3-year composite of cardiovascular death, myocardial infarction, coronary artery revascularization, hospitalization for heart failure treatment, or non-fatal stroke.
Secondary efficacy endpoint	3-year composite of all-cause death, coronary or peripheral revascularization, hospitalization for cardiovascular events, or non-fatal stroke.	3-year composite of all-cause death, myocardial infarction, coronary artery revascularization, hospitalization for heart failure treatment, or non-fatal stroke.

2 청구데이터의 활용 – RCT 가 불가능한 치료의 장기 효과

ESC European Society of Cardiology
European Heart Journal (2020) 41, 3521–3529
doi:10.1093/eurheartj/ehaa376

CLINICAL RESEARCH
Acute Coronary Syndromes

Long-term β-blocker therapy and clinical outcomes after acute myocardial infarction in patients without heart failure: nationwide cohort study

Jihoon Kim[1†], Danbee Kang[2,3†], Hyejeong Park[2], Minwoong Kang[2,3], Taek Kyu Park[1], Joo Myung Lee[1], Jeong Hoon Yang[1], Young Bin Song[1], Jin-Ho Choi[1], Seung-Hyuk Choi[1], Hyeon-Cheol Gwon[1], Eliseo Guallar[2,3,4], Juhee Cho[2,3*], and Joo-Yong Hahn[1*]

[1]Division of Cardiology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Korea; [2]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Korea; [3]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, 81 Irwon-Ro, Gangnam-gu, Seoul 06351, Korea; and [4]Department s of Epidemiology and Medicine, Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA

Received 5 December 2019; revised 5 March 2020; editorial decision 22 April 2020; accepted 22 April 2020; online publish-ahead-of-print 15 June 2020

See page 3530 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa436)

Aims To investigate the association between long-term β-blocker therapy and clinical outcomes in patients without heart failure (HF) after acute myocardial infarction (AMI).

Method and results Between 2010 and 2015, a total of 28 970 patients who underwent coronary revascularization for AMI with β-blocker prescription at hospital discharge and were event-free from death, recurrent myocardial infarction (MI), or HF for 1 year were enrolled from Korean nationwide medical insurance data. The primary outcome was all-cause death. The secondary outcomes were recurrent MI, hospitalization for new HF, and a composite of all-cause death, recurrent MI, or hospitalization for new HF. Outcomes were compared between β-blocker therapy for ≥1 year (*N* = 22 707) and β-blocker therapy for <1 year (*N* = 6263) using landmark analysis at 1 year after index MI. Compared with patients receiving β-blocker therapy for <1 year, those receiving β-blocker therapy for ≥1 year had significantly lower risks of all-cause death [adjusted hazard ratio (HR) 0.81; 95% confidence interval (CI) 0.72–0.91] and composite of all-cause death, recurrent MI, or hospitalization for new HF (adjusted HR 0.82; 95% CI 0.75–0.89), but not the risks of recurrent MI or hospitalization for new HF. The lower risk of all-cause death associated with persistent β-blocker therapy was observed beyond 2 years (adjusted HR 0.86; 95% CI 0.75–0.99) but not beyond 3 years (adjusted HR 0.87; 95% CI 0.73–1.03) after MI.

Conclusion In this nationwide cohort, β-blocker therapy for ≥1 year after MI was associated with reduced all-cause death among patients with AMI without HF.

Keywords Myocardial infarction • β-blocker • Outcomes

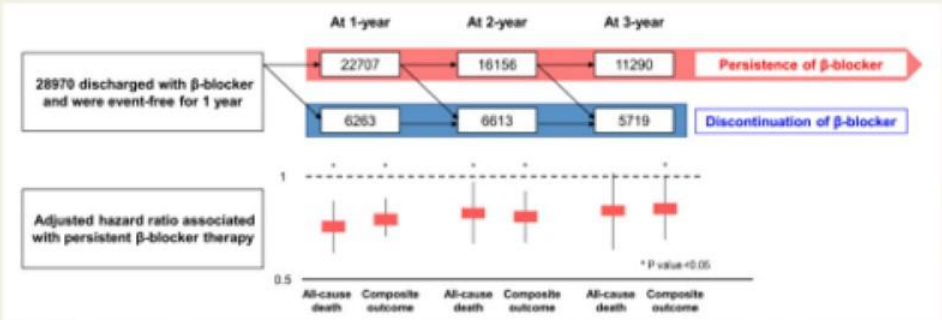


Figure 4 Persistent β-blocker therapy and clinical outcomes after myocardial infarction. A composite outcome includes all-cause death, recurrent myocardial infarction, or hospitalization for new heart failure.

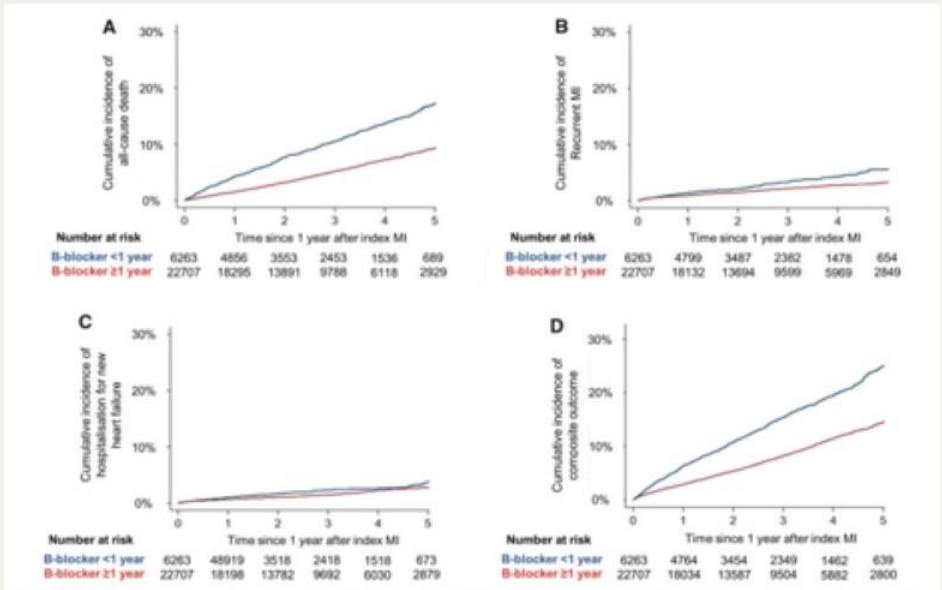


Figure 2 Cumulative incidences of clinical outcomes since 1 year after myocardial infarction. (*A*) All-cause death, (*B*) recurrent MI, (*C*) hospitalization for new heart failure, and (*D*) a composite of all-cause death, recurrent MI, or hospitalization for new heart failure. MI, myocardial infarction.

2 청구데이터의 활용 – RCT 가 불가능한 치료의 장기 효과

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Radiology

Use of Gadoxetic Acid–enhanced Liver MRI and Mortality in More than 30000 Patients with Hepatocellular Carcinoma: A Nationwide Analysis

Tae Wook Kang, MD • Sun-Young Kong, MD* • Danbee Kang, PhD • Min Woong Kang, MS • Young Kon Kim, MD • Seong Hyun Kim, MD • Dong Hyun Sinn, MD • Young Ae Kim, PhD • Kui Son Choi, PhD • Eun Sook Lee, MD • Sang Myung Woo, MD • Joung Hwan Back, PhD • Eliseo Guallar, DrPH • Juhee Cho, PhD*

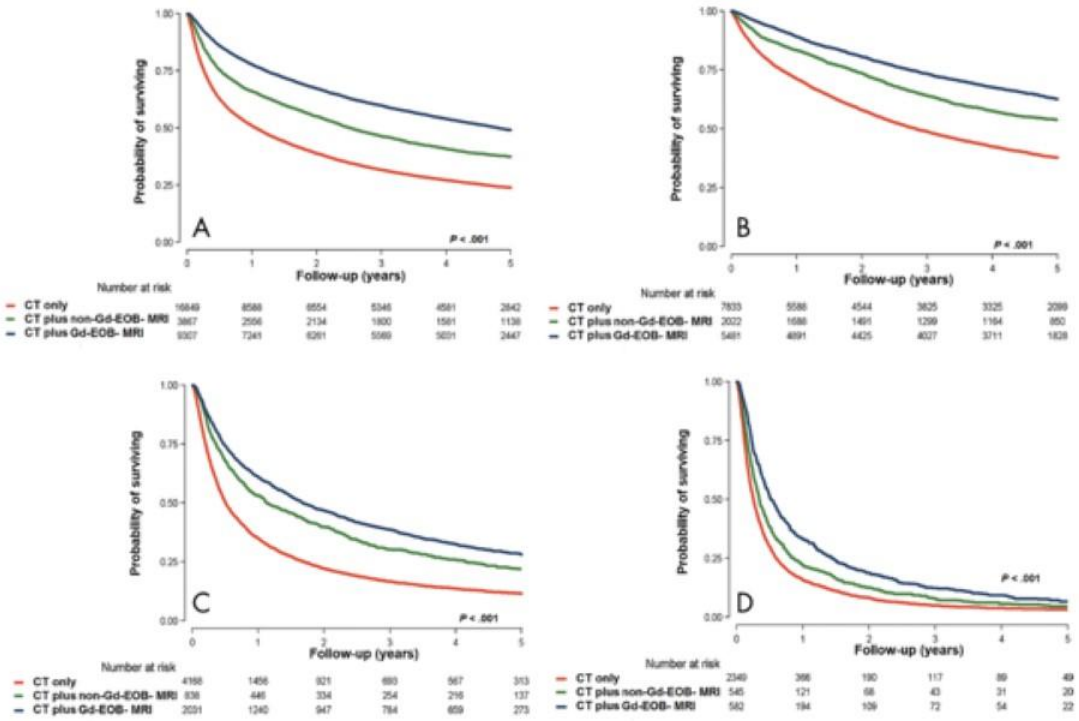


Figure 2: Graphs show cumulative survival from the time of diagnosis according to initial diagnostic imaging technique and Surveillance, Epidemiology, and End Results summary stage. *A*, Overall survival and survival according to, *B*, localized disease, *C*, regional disease, and, *D*, distant disease. Gd-EOB-MRI = gadoxetic acid–enhanced MRI.

2 청구데이터의 활용 – RCT가 어려운 대상

Circulation
Volume 153, Issue 7, 17 February 2026; Pages 504-515
https://doi.org/10.1161/CIRCULATIONAHA.125.078919

ORIGINAL RESEARCH ARTICLE

Association of Statin Discontinuation in Pregnancy With Maternal Cardiovascular Health and Birth Outcomes: A Nationwide Cohort Study

Yongtai Cho, PharmD, Danbee Kang, PhD, HyunJoo Lim, PharmD, Hyesung Lee, PhD, Eun-Young Choi, PharmD, PhD, Ju-Young Shin, PhD, and Ki Hong Choi, MD, PhD

Background: Discontinuing statin therapy before pregnancy remains challenging especially in high-risk women. We evaluated the risks of maternal cardiovascular gestational, and fetal outcomes associated with continuing versus discontinuing statin therapy before the last menstrual period (LMP).

Methods: We conducted a nationwide cohort study using data from the National Health Insurance Database of South Korea collected between 2009 and 2023. Women who used statins for 12 to 24 weeks before their LMP between 2010 and 2022 were stratified by whether they discontinued statins before their LMP. Maternal cardiovascular outcomes were major adverse cardiovascular and cerebrovascular events (MACCE), a composite of myocardial infarction, stroke, coronary revascularization, and cardiovascular death. Gestational and fetal outcomes included preterm delivery, pre-eclampsia/eclampsia other hypertensive disorders of pregnancy, gestational diabetes, nonlive birth, major congenital malformations, and low birth weight. Propensity scores were estimated from potential confounders, and overlap weighting was applied to control for confounding factors. The weighted hazard ratio for MACCE was estimated using a Cox proportional hazards model. Weighted risk ratios for gestational outcomes were estimated using

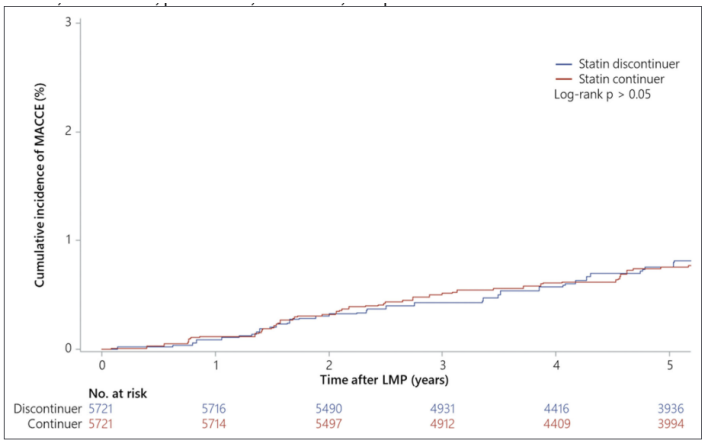


Figure 2. Propensity score–weighted cumulative incidence of MACCE by statin continuation status. Propensity score overlap–weighted cumulative incidence curves of MACCE after the LMP are shown for women who discontinued statins before the LMP (discontinuers, blue line) and those who continued statin therapy into pregnancy (continuers, red line). Group differences were evaluated using the log-rank test. LMP indicates last menstrual period; and MACCE, major adverse cardiac and cerebrovascular events.

2 청구데이터의 활용 – 건강행동

Alcohol Intake and Mortality in Patients With Chronic Viral Hepatitis: A Nationwide Cohort Study

Dong Hyun Sinn, MD[1], Danbee Kang, PhD[2], Eliseo Guallar, PhD, MPh[3,4], Yoosoo Chang, MD, PhD[2,5,6], Seungho Ryu, MD, PhD[2,5,6], Di Zhao, PhD[4], Yun Soo Hong, MD[4], Juhee Cho, PhD[2,3,4] and Geum-Youn Gwak, MD, PhD[1]

INTRODUCTION: **We evaluated the association between alcohol intake and all-cause and cause-specific mortality in subjects with chronic viral hepatitis, using nationwide population-based cohort study.**

METHODS: **A total of 364,361 men and women aged 40–84 years who underwent health screening examination between January 2002 and December 2013 that included assessment of frequency and amount of alcohol consumption were assessed for all-cause and cause-specific mortality.**

RESULTS: **In participants without chronic viral hepatitis, the fully adjusted hazard ratios (HRs) for all-cause mortality comparing light, moderate, and heavy drinkers with nondrinkers were 0.92 (95% confidence interval [CI] 0.87–0.98), 1.08 (95% CI 1.01–1.16), and 1.51 (95% CI 1.33–1.72), respectively. In participants with chronic viral hepatitis, the corresponding HRs were 1.19 (95% CI 1.05–1.36), 1.23 (95% CI 1.06–1.43), and 1.69 (95% CI 1.28–2.24), respectively (*P* value for alcohol intake by chronic viral hepatitis interaction <0.001). Compared with participants without chronic viral hepatitis, those with chronic viral hepatitis had substantially elevated liver cancer or liver disease (HR 10.85, 95% CI 9.74–12.09) and extrahepatic cancer mortality (HR 1.37, 95% CI 1.26–1.49). In patients with chronic viral hepatitis, the high mortality due to liver cancer or liver disease and the positive association of alcohol intake with liver cancer or liver disease mortality explained the positive association of alcohol intake with all-cause mortality.**

DISCUSSION: **Even light to moderate alcohol intake was associated with increased all-cause mortality in individuals with chronic viral hepatitis. Clinicians and public health campaigns should advise against any amount of alcohol intake in individuals with chronic viral hepatitis.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B698

Am J Gastroenterol 2021;116:329–335. https://doi.org/10.14309/ajg.0000000000000966

AM J Gastroeterol (2021)

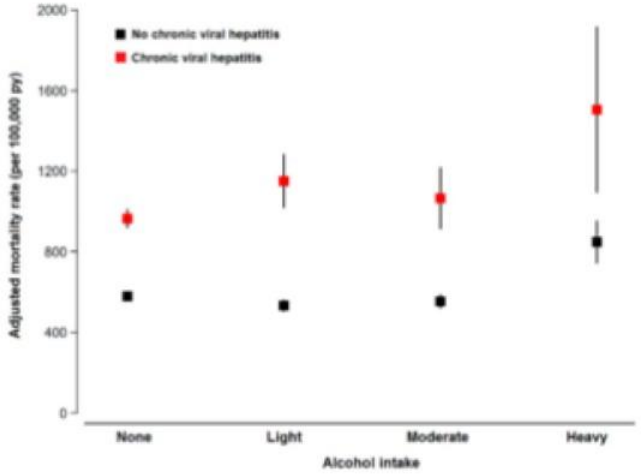


Figure 1. Multivariable-adjusted all-cause mortality rates by alcohol intake and chronic viral hepatitis status. Marginally adjusted mortality rates were calculated from a Poisson regression model adjusted for age, sex, body mass

Table 2. Multivariable-adjusted HRs for all-cause mortality by chronic viral hepatitis status

Alcohol intake	Chronic viral hepatitis		*P* for interaction
	No HR (95% CI)	Yes HR (95% CI)	
None	Reference	Reference	0.002
Light	0.92 (0.87, 0.98)	1.19 (1.05, 1.36)	
Moderate	1.08 (1.01, 1.16)	1.23 (1.06, 1.43)	
Heavy	1.51 (1.33, 1.72)	1.69 (1.28, 2.24)	

HRs and 95% CIs were obtained from proportional hazards models with age as time scale and adjusted for sex, body mass index (underweight, normal, overweight, obese, and unknown), smoking status (never, ever, or unknown), Charlson Comorbidity Index, income percentile (≤30th, >30th–≤70th, and >70th), residential area (metropolitan and rural), and antiviral treatment. CI, confidence interval; HR, hazard ratio.

Association Between Regular Moderate to Vigorous Physical Activity Initiation Following COPD Diagnosis and Mortality

An Emulated Target Trial Using Nationwide Cohort Data

Taeyun Kim, MD; Hyunsoo Kim, MS; Sunga Kong, PhD; Sun Hye Shin, MD, PhD; Juhee Cho, PhD; Danbee Kang, PhD; and Hye Yun Park, MD, PhD

BACKGROUND: Moderate to vigorous physical activity (MVPA) in patients with COPD aff their overall health outcomes, including symptom relief and improved quality of However, the magnitude of the effect of MVPA initiation on real-world clinical outcomes not been well investigated.

RESEARCH QUESTION: How does MVPA initiation affect mortality and severe exacerbatio patients who have not engaged in MVPA prior to COPD diagnosis?

STUDY DESIGN AND METHODS: This study included patients with COPD aged ≥ 40 years were not performing MVPA prior to COPD diagnosis and who had at least one he screening visit prior to and following their COPD diagnosis between January 1, 2010, December 31, 2018. The main exposure was MVPA, defined as vigorous aerobic exercis 20 min per day on ≥ 3 days per week or moderate aerobic exercise > 30 min per day o 5 days per week. The primary end point was all-cause mortality, and the secondary end p was initial severe exacerbation as the time to event following COPD diagnosis.

RESULTS: In total, 110,097 person-trials were included (27,564 MVPA increases and 82, control groups). No differences were observed between the covariates following match The adjusted hazards ratio of all-cause mortality for the MVPA group compared with control group was 0.84 (95% CI, 0.79-0.89). In the subgroup analysis, patients aged > years, female patients, those who had never smoked, and patients with a higher Charl Comorbidity Index score displayed a stronger effect of MVPA on reducing mortality t younger male patients, those who had ever smoked, and patients with a lower Charl Comorbidity Index score ($P_{interaction} < .05$). The fully adjusted hazards ratio for the risl severe exacerbation (MVPA group vs control) was 0.90 (95% CI, 0.87-0.94).

INTERPRETATION: Initiation of MVPA can potentially reduce mortality and severe exa bations in patients with COPD, although personalized interventions and further clinical t are necessary.

CHEST 2024; 165(1):84

KEY WORDS: COPD; exacerbation; mortality; physical activity

ABBREVIATIONS: CCI = Charlson Comorbidity Index; HR = hazard ratio; ICD-10 = International Classification of Diseases, Tenth Revision; ICS = inhaled corticosteroids; K-NHIS = Korean National Health Insurance System; MVPA = moderate to vigorous physical activity; PA = physical activity; SMD = standardized mean difference

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (T. K., S. H. S., and H. Y. P.), Department of Internal Medicine, Samsung Medical Center, and Department of Clinical Research Design and Evaluation (J. C. and D. K.), SAIHST, Sungkyunkwan University, Seoul, South Korea; and Center for Clinical Epidemiology (H. K., S. K., J. C., and D. K.) and Patient-Centered Outcomes Research Institute (S. K.), Samsung Medical Center, Seoul, South Korea.

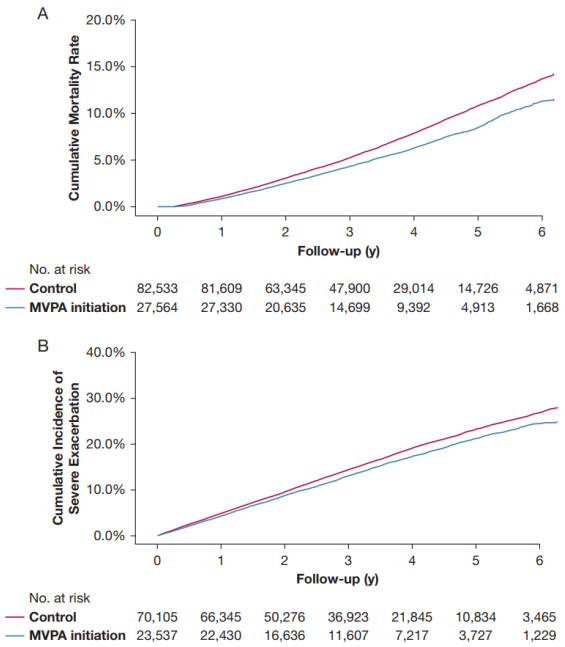
Drs T. Kim and H. Kim contributed equally to this article.

Drs Kang and Park contributed equally to this article.

CORRESPONDENCE TO: Hye Yun Park, MD, PhD; email: hyeyunpark@skku.edu

DOI: https://doi.org/10.1016/j.chest.2023.07.017

Figure 2 – *A, B. Kaplan-Meier curve for incidence of mortality (N = 110,097) (A) and severe exacerbation (N = 93,642) (B). MVPA = moderate to vigorous physical activity.*



2 청구데이터의 활용 – 건강행동

ESC European Society of Cardiology
European Heart Journal (2024) **00**, 1–12
https://doi.org/10.1093/eurheartj/ehae705

CLINICAL RESEARCH
Interventional cardiology

Prognosis after switching to electronic cigarettes following percutaneous coronary intervention: a Korean nationwide study

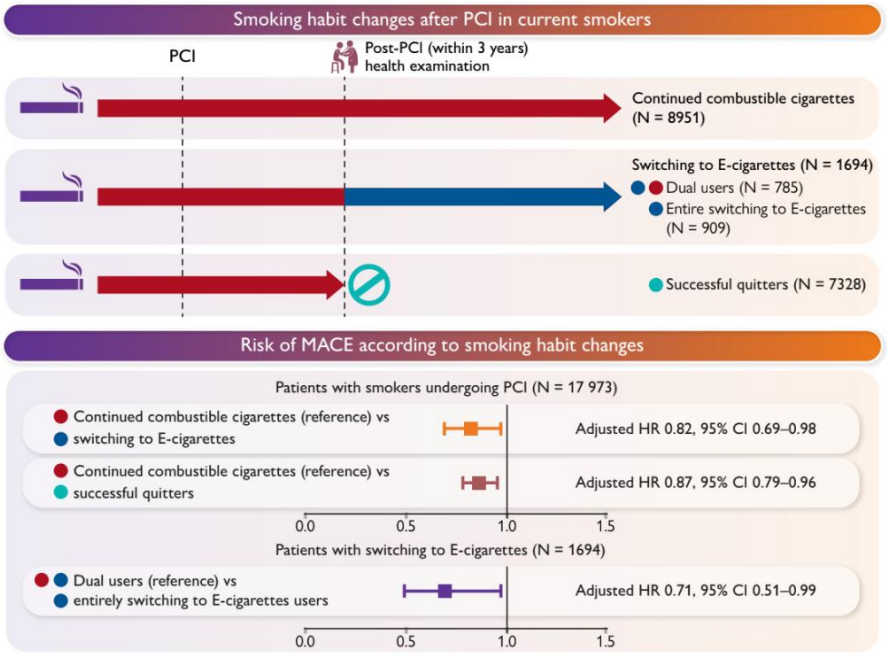
Danbee Kang [1,2], Ki Hong Choi [3,*], Hyunsoo Kim[1], Hyejeong Park[1], Jihye Heo[1,2], Taek Kyu Park[3], Joo Myung Lee [3], Juhee Cho [1,2], Jeong Hoon Yang [3], Joo-Yong Hahn[3], Seung-Hyuk Choi[3], Hyeon-Cheol Gwon[3], and Young Bin Song [3]

[1]Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, Republic of Korea; and [3]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 06351, Republic of Korea

Received 21 April 2024; revised 30 June 2024; accepted 30 September 2024

Abstract

Background and Aims	Despite the increasing popularity of electronic cigarettes (E-cigarettes), the prognostic impact of switching to E-cigarettes in smokers with coronary artery disease who have undergone percutaneous coronary intervention (PCI) remains unclear.
Methods	Using a nationwide cohort from the Korean National Health Insurance database, 17 973 adults (≥20 years) identified as smokers (based on a health screening examination within 3 years before PCI) who underwent health screening within 3 years after PCI were enrolled to determine changes in smoking habits. Patients were classified as continued combustible cigarette users, successful quitters, or switchers to E-cigarettes. The group switching to E-cigarettes was further divided into dual users (using both combustible and E-cigarettes) and those exclusively using E-cigarettes. Primary outcomes included major adverse cardiac events (MACEs), a composite of all-cause death, spontaneous myocardial infarction, and repeat revascularization.
Results	Among the total population, 8951 patients (49.8%) continued using combustible cigarettes, 1694 (9.4%) were switched to E-cigarettes, and 7328 (40.7%) successfully quit smoking after PCI. During a median follow-up of 2.4 years, the cumulative incidence of MACE was lower among E-cigarette switchers (10%) or quitters (13.4%) than among continued combustible cigarette users (17%). When continued combustible cigarette users were used as the reference, the multivariable-adjusted hazard ratios with 95% confidence intervals for MACE were 0.82 (0.69–0.98) for switchers to E-cigarettes and 0.87 (0.79–0.96) for successful quitters. Compared with dual users, entirely switching to E-cigarettes was associated with a significantly lower MACE risk (hazard ratio 0.71; 95% confidence interval 0.51–0.99).
Conclusions	Among smokers who underwent PCI for coronary artery disease, switching to E-cigarette use (particularly complete transition) or quitting smoking was associated with reduced MACE risk than with continued combustible cigarette use.
Clinical Trial Registration	ClinicalTrials.gov NCT06338761



2 청구데이터의 활용 – 의료 resource 와 outcome

RESEARCH Open Access

Association between intensive care unit nursing grade and mortality in patients with cardiogenic shock and its cost-effectiveness

Ki Hong Choi[1†], Danbee Kang[2,3†], Jin Lee[2,3], Hyejeong Park[3], Taek Kyu Park[1], Joo Myung Lee[1], Young Bin Song[1], Joo-Yong Hahn[1], Seung-Hyuk Choi[1], Hyeon-Cheol Gwon[1], Juhee Cho[2,3*] and Jeong Hoon Yang[1,4*]

Abstract

Background Despite the high workload of cardiac intensive care unit (ICU), there is a paucity of evidence on the association between nurse workforce and mortality in patients with cardiogenic shock (CS). This study aimed to evaluate the prognostic impact of the ICU nursing grade on mortality and cost-effectiveness in CS.

Methods A nationwide analysis was performed using the K-NHIS database. Patients diagnosed with CS and admitted to the ICU at tertiary hospitals were enrolled. ICU nursing grade was defined according to the bed-to-nurse ratio: grade1 (bed-to-nurse ratio < 0.5), grade2 (0.5 ≤ bed-to-nurse ratio < 0.63), and grade3 (0.63 ≤ bed-to-nurse ratio < 0.77) or above. The primary endpoint was in-hospital mortality. Cost-effective analysis was also performed.

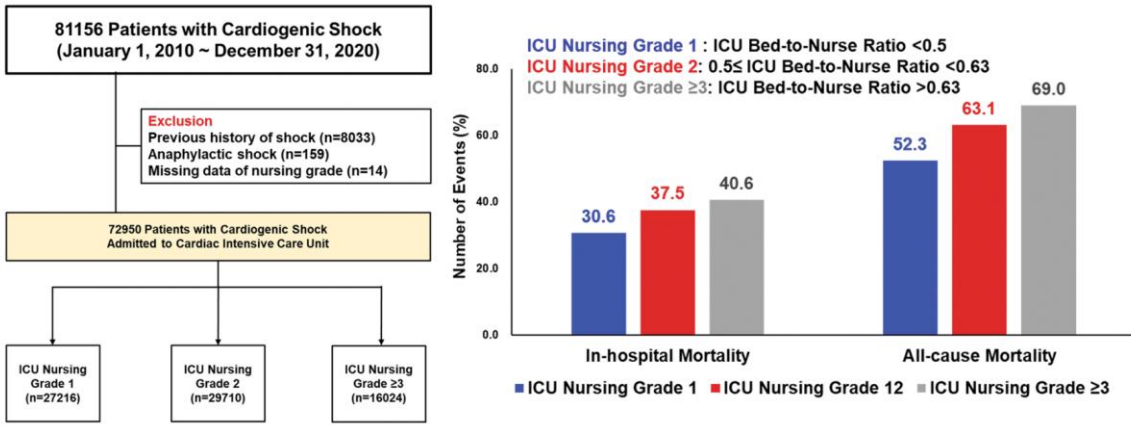
Results Of the 72,950 patients with CS, 27,216 (37.3%) were in ICU nursing grade 1, 29,710 (40.7%) in grade 2, and 16,024 (22.0%) in grade ≥ 3. The adjusted-OR for in-hospital mortality was significantly higher in patients with grade 2 (grade 1 vs. grade 2, 30.6% vs. 37.5%, adjusted-OR 1.14, 95% CI1.09–1.19) and grade ≥ 3 (40.6%) with an adjusted-OR of 1.29 (95% CI 1.23–1.36) than those with grade 1. The incremental cost-effectiveness ratio of grade1 compared with grade 2 and ≥ 3 was $25,047/year and $42,888/year for hospitalization and $5151/year and $5269/year for 1-year follow-up, suggesting that grade 1 was cost-effective. In subgroup analysis, the beneficial effects of the high-intensity nursing grade on mortality were more prominent in patients who received CPR or multiple vasopressors usage.

Conclusions For patients with CS, ICU grade 1 with a high-intensity nursing staff was associated with reduced mortality and more cost-effectiveness during hospitalization compared to grade 2 and grade ≥ 3, and its beneficial effects were more pronounced in subjects at high risk of CS.

Keywords Cardiogenic shock, Intensive care unit, Nurse staffing, Mortality, Cost-effectiveness

†Ki Hong Choi and Danbee Kang contributed equally to this work.

Graphical abstract



3. 청구데이터 활용 연구 방법

3 청구데이터 활용 연구 방법

○ 절차

STEP 1.
연구 주제 선정
- Outcome,
- exposure
- 연구대상자 선정

STEP 2.
주요변수생성
- 조작적 정의 이용

STEP 3.
DATA 분포 검토
Descriptive analysis
Subgroup analysis

STEP 4.
가설검증 및 확인
- Statistical analysis

1. 분석 전 "선" 연구설계
- 내가 궁금한 내용을 연구화 하기 !

Planning - 가설확인

1) 개념화와 조작화 필요: 사람에 따라 동일한 개념에 대해 서로 다른 생각을 가질 수 있기 때문에 주요 변수에 대한개념 정의가 필요함.

ex) 건강 = 질병이 없는 상태?, 모든 측면의 안녕

2) 조작적 정의 필요: 개념을 관찰하고 측정할 수 있도록 하기 위한 구체적 정의 필요.

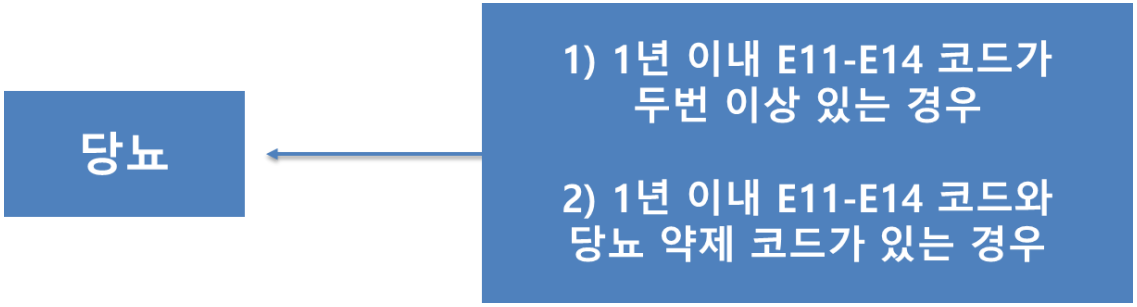
ex) 건강 = 동반질환의 개수

= WHO 에서 개발한 삶의 질 도구 이용?

Planning - 가설확인

- 가설 확인: 암환자가 일반인보다 당뇨병을 경험할 위험이 더 높다.
  - Participants
  - Outcome
  - Exposure

- 조작적 정의 (Operational definition)
  - 양적 연구에서는 개념을 수량화 하기 위한 조작적 정의가 필요.
  - 연구에서 보고자 하는 outcomes을 현재 측정 값 또는 측정가능한 값을 이용하여 정의



예. 질병분류에 따른 당뇨병 환자 수 차이 (2009 국민건강영양조사)

- 총 10,533명 중
  - Q1: 당신은 당뇨병을 앓고 있습니까? 541명
  - Q2: 의사진단에 의한 당뇨병을 앓고 있습니까? 579명
  - Q3: 당뇨병으로 인해 약물치료를 받고 있습니까? 502명
  - 공복혈당이 126mg/dL이상? 458명
  - HbA1c 6.5이상? 457명
  - 공복혈당+ HbA1c 두 가지 중 하나 만족? 580명

Lee et al. BMC Medicine (2018) 16:178
https://doi.org/10.1186/s12916-018-1159-7

BMC Medicine

RESEARCH ARTICLE Open Access

Racial differences in comorbidity profile among patients with chronic obstructive pulmonary disease

Hyun Lee[1], Sun Hye Shin[2], Seonhye Gu[3], Di Zhao[5], Danbee Kang[3,4], Yeong Rae Joi[3], Gee Young Suh[2], Roberto Pastor-Barriuso[6], Eliseo Guallar[4,5], Juhee Cho[3,4,5†] and Hye Yun Park[2*†]

Definitions

COPD was defined based on pre-bronchodilator FEV_1 / FVC < 0.7, and COPD severity was classified as mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), or severe-to-very severe ($FEV_1 < 50\%$ predicted) [1]. Height and weight were measured and body

Table 1 Characteristics of participants with COPD aged 40–79 by race and ethnicity, U.S. NHANES 2007–2012 and Korea NHANES 2007–2015[a]

	U.S. NHANES			Korea NHANES	
	Non-Hispanic White ($n = 944$)	Non-Hispanic Black ($n = 324$)	Hispanic[b] ($n = 227$)	Korean ($n = 3808$)	p value
Age, years	59.8(0.4)	59.6 (0.7)	59.6 (0.8)	63.6 (0.2)	< 0.001
Age group, years					< 0.001
40–49	18.7 (1.7)	20.7 (2.9)	19.7 (3.1)	11.3 (0.7)	
50–59	31.2 (2.2)	30.9 (2.6)	29.9 (3.9)	23.2 (0.9)	
60–69	30.3 (2.4)	24.1 (1.8)	32.0 (3.0)	31.2 (0.9)	
70–79	19.8 (1.3)	24.2 (2.5)	18.3 (2.7)	34.3 (1.0)	
Men, %	59.1 (2.4)	60.2 (2.3)	69.2 (4.2)	73.8 (0.9)	< 0.001
BMI, kg/m^2	27.7 (0.2)	27.8 (0.4)	28. 6 (0.4)	23.7 (0.1)	< 0.001
BMI group					0.023
Underweight	1.9 (0.5)	3.1 (1.2)	0	2.7 (0.4)	
Normal	32.3 (1.6)	35.1 (2.8)	27.4 (3.4)	38.9 (1.1)	
Overweight	37.8 (1.5)	33.4 (2.3)	41.9 (3.7)	27.6 (0.9)	
Obese	27.9 (1.4)	28.4 (2.6)	30.7 (3.8)	30.7 (1.0)	
Smoking					< 0.001
Current	33.5 (2.4)	42.4 (3.4)	26.4 (2.8)	41.6 (1.0)	
Former	39.9 (2.1)	26.4 (2.2)	35.5 (2.9)	27.9 (0.9)	
Never	26.6 (2.1)	31.3 (2.8)	38.1 (3.3)	30.5 (1.0)	

OPEN ACCESS

Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study

Hye Yun Park,[1] Danbee Kang,[2,3] Sun Hye Shin,[1] Kwang-Ha Yoo,[4] Chin Kook Rhee,[5] Gee Young Suh,[1] Hojoong Kim,[1] Young Mog Shim,[6] Eliseo Guallar,[7] Juhee Cho,[2,3,7] O Jung Kwon[1]

For numbered affiliations see end of article.

Correspondence to
Dr Juhee Cho, Center for Clinical Epidemiology, Samsung Medical Center, Seoul 06351, South Korea; jcho@skku.edu

HYP and DK contributed equally. JC and OJK contributed equally.

Received 20 June 2019
Revised 25 November 2019
Accepted 31 December 2019
Published Online First
2 April 2020

ABSTRACT

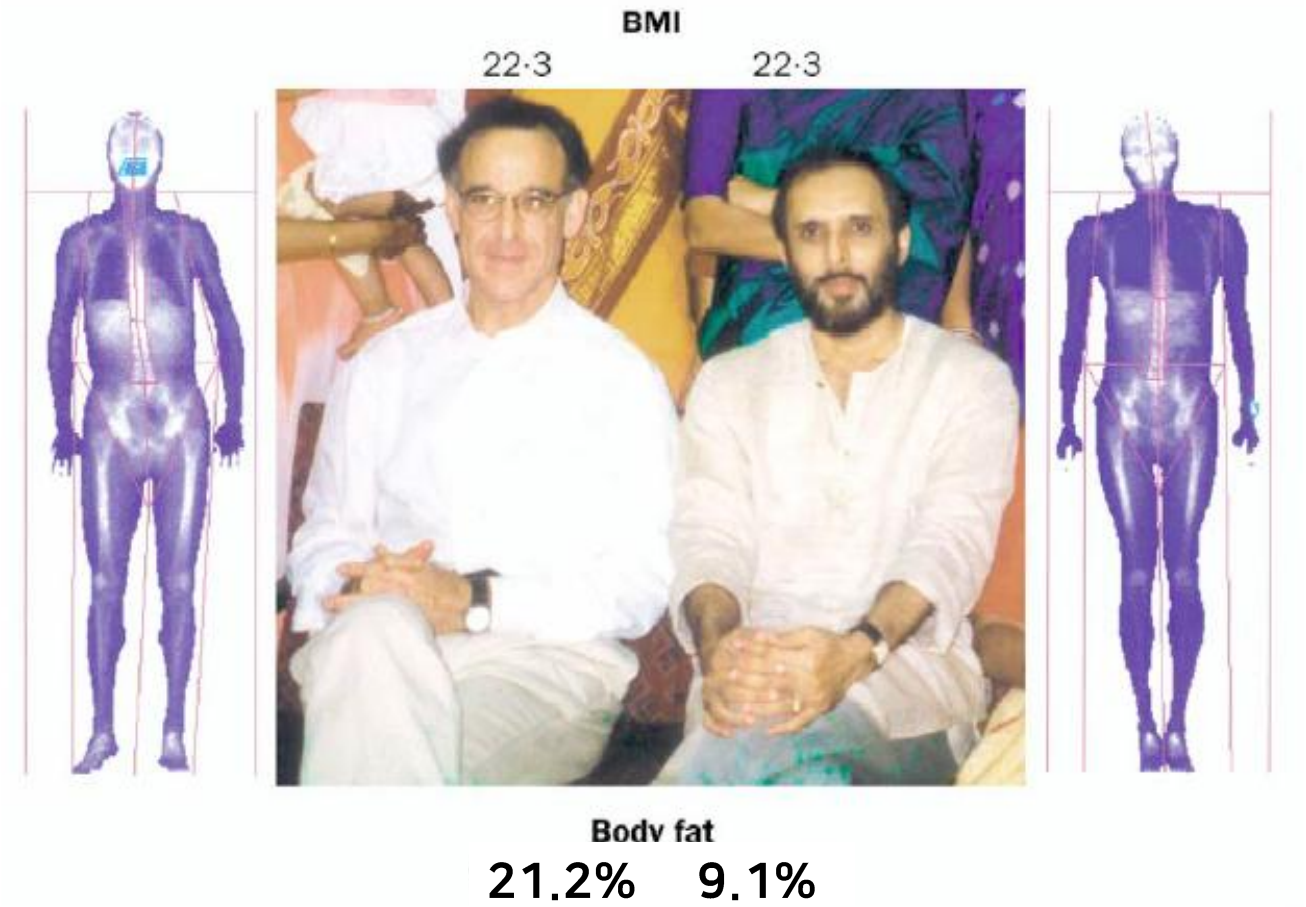
There has been limited evidence for the association between chronic obstructive pulmonary disease (COPD) and the incidence of lung cancer among never smokers. We aimed to estimate the risk of lung cancer incidence in never smokers with COPD, and to compare it with the risk associated with smoking. This cohort study involved 338 548 subjects, 40 to 84 years of age with no history of lung cancer at baseline, enrolled in the National Health Insurance Service National Sample Cohort. During 2 355 005 person-years of follow-up (median follow-up 7.0 years), 1834 participants developed lung cancer. Compared with never smokers without COPD, the fully-adjuste
smokers

We included all men and women, 40 to 84 years of age, who underwent at least one health screening examination provided by the NHIS during the study period (n=370 617). We excluded participants who had cancer (n=8999) before the first screening exam (baseline), or who had missing values for body mass index or smoking status at the baseline exam (n=23 070). The final sample size was 338 548 participants (146 996 men and 191 552 women). The Institutional Review Board of the Samsung Medical Centre approved this study and waived the requirement for informed consent as we used only de-identified data.

talisation with a C33 or C34 code.[8] COPD was defined as the presence of J43-J44 (except J43.0) codes and use of COPD medications at least twice within a year.[9] Smoking habits were measured by

Baseline characteristic	Overall (n=338 548)	COPD*		P value
		No (n=326 169)	Yes (n=12 379)	
Sex				<0.001
Male	146 996 (43.4)	140 581 (43.1)	6415 (51.8)	
Female	191 552 (56.6)	184 588 (56.9)	5964 (48.2)	
Smoking status				<0.001
Never	241 633 (71.4)	233 266 (71.5)	8367 (67.6)	
Past	21 818 (6.4)	21 016 (6.4)	802 (6.5)	
Current	75 097 (22.2)	71 887 (22.0)	3210 (25.9)	

Measurement



Choice of appropriate assessment measures

EORTC-C30, social functioning

* 지난 한 주를 기준으로 답변하여 주십시오.		전혀 아니다	약간 그렇다	꽤 그렇다	매우 그렇다
6	일을 하거나 기타 일상생활을 영위하는데 한계를 느낀 적이 있습니까?	1	2	3	4
7	취미생활이나 여가활동을 하는데 있어 한계를 느낀 적이 있습니까?	1	2	3	4

Weak to moderate correlation, r=0.10-0.50

FACT-G, social well-being

		전혀 그렇지 않다	조금 그렇다	보통이다	다소 그렇다	매우 그렇다
	사회/가족 영역					
1.	친구들과 가까워지는 듯한 느낌이 든다.	0	1	2	3	4
2.	정서적으로 가족들의 따뜻한 보살핌을 받는다.	0	1	2	3	4
3.	친구들로부터 도움을 받는다.	0	1	2	3	4
4.	내 가족들은 내 병을 받아들였다.	0	1	2	3	4
5.	내 병에 대한 가족들의 대화에 만족한다.	0	1	2	3	4
6.	배우자와 가깝게 느낀다	0	1	2	3	4

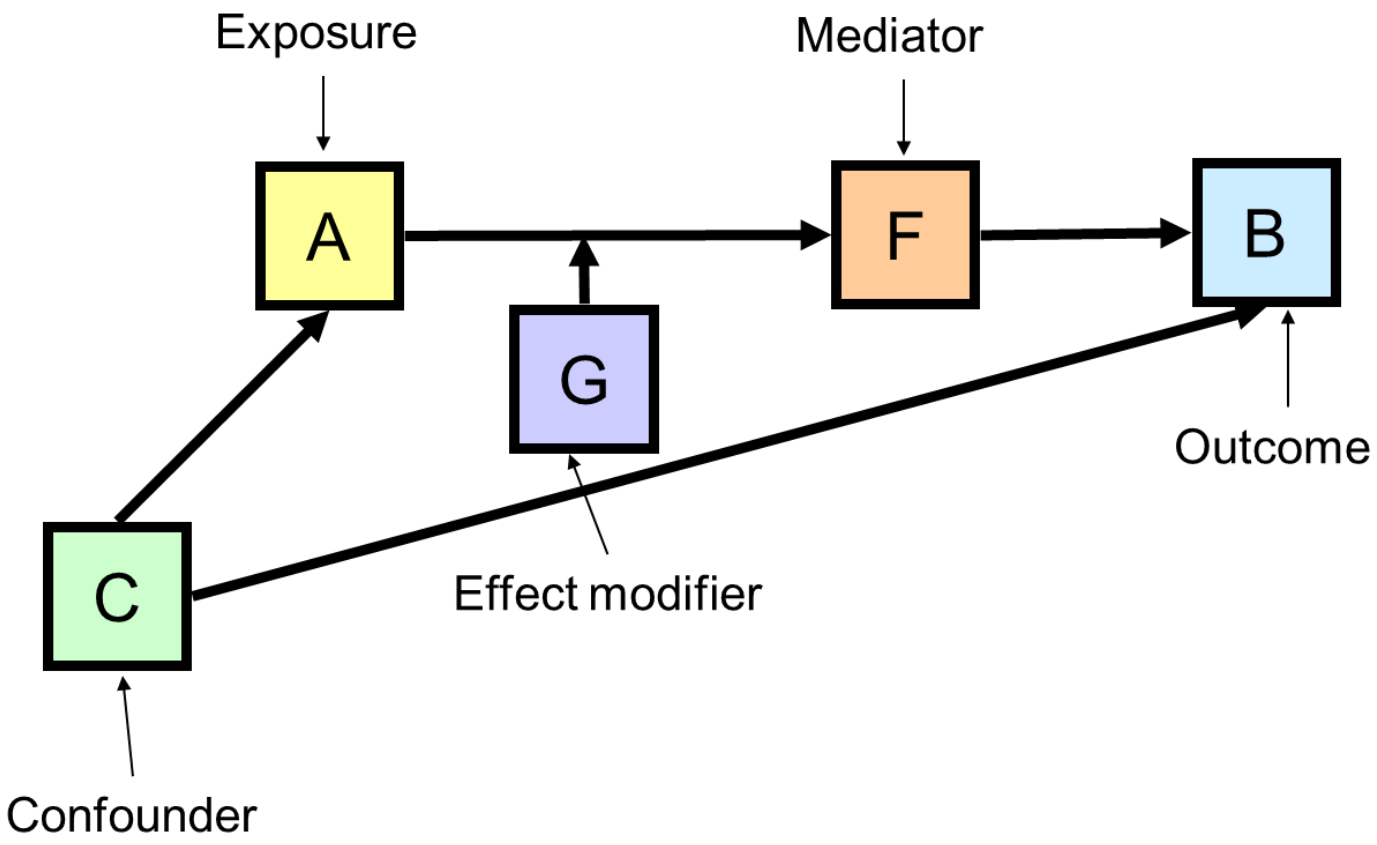
Luckett T. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. Annals of Oncology 22: 2179–2190, 2011

가설확인에 따른 변수정의 – include all variables

- List information/variables needed for the study
  - Exposure
  - Outcome
  - Confounder BASED ON
    - LITERARUE REVIEW +
    - STAFF'S RECOMMENDATIONS
    - YOUR CLINICAL EXPERIENCE (IDEA)
  - Demographics
  - Clinical – diagnosis, treatment, remission
  - Behavioral
  - Others

가설확인에 따른 변수정의 – include all variables

- List information/variables needed for the study



PICO

- 잘 만들어진 임상 질문에는
  - 환자 혹은 문제(patient or problem),
  - 치료법(intervention),
  - 비교법(comparator)과
  - 예상되는 치료의 결과(outcome)에 대한 내용을 포함
- 이를 흔히 PICO 형식이라는 용어로 줄여 부름.

PICOTS-SD

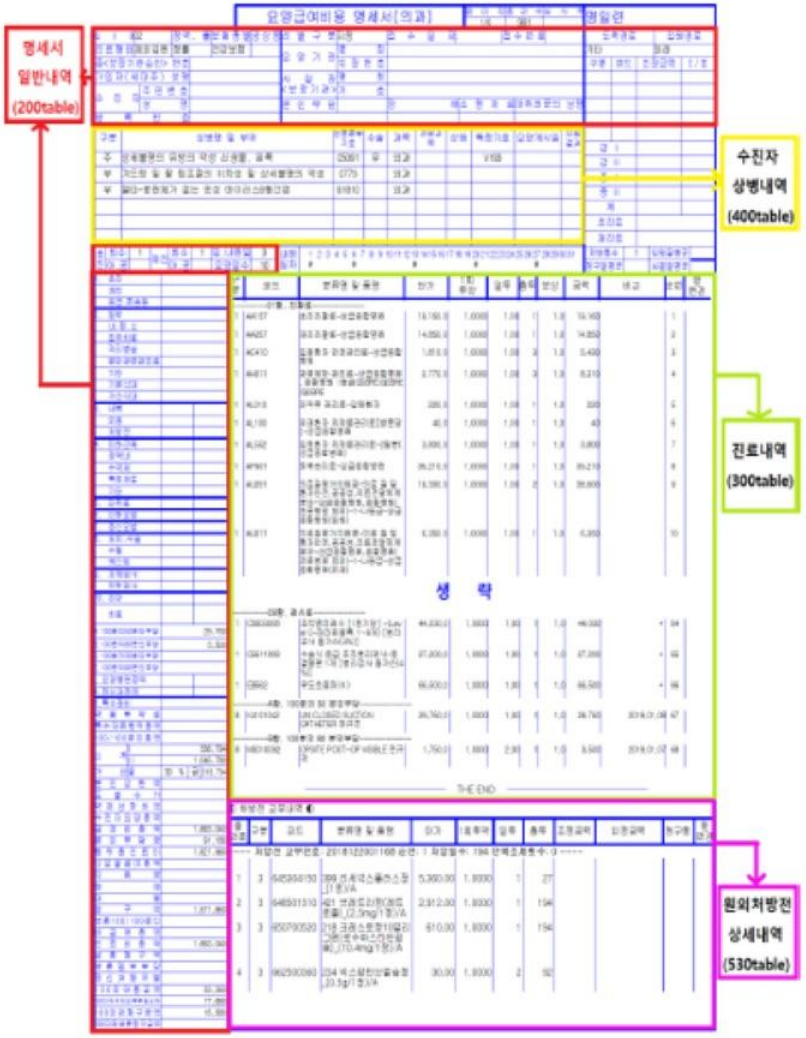
- PICO
- + Time : 보고자 하는 결과변수의 추적관찰 기간
- + Setting : 어느 세팅에서 이루어진 임상연구인지?
- + Study design : 연구 설계

2. 내 연구에 맞는 데이터 확인

	건강보험심사평가원	건강보험공단
데이터 내용	명세서일반 진료내역 수신자상병 원외처방전교부상세 요양기관정보	명세서일반 진료내역 수신자상병 원외처방전교부상세 요양기관정보 자격 (사망 등) 건강검진
데이터 종류	• 표본* - 1년단위 코호트 등 • 맞춤형 – 연구자 선택 (단, `07~ 현 시점 기준 8개월 전까지 자료)	• 표본* – 06자격기준 `02-`20 코호트 등 • 맞춤형 – 연구자 선택 (단, 약제/ 재료 등은 코드단위까지 신청해야 함)
신청 방법	인터넷 신청 (3개월 이상 소요)	인터넷 신청 (6개월 이상 소요)
무료/유료	유료 (월 70만원)	
연구 방법	표본 - CD 맞춤형 - 원격접속	표본 – 원격접속 맞춤형 – 분석센터 방문

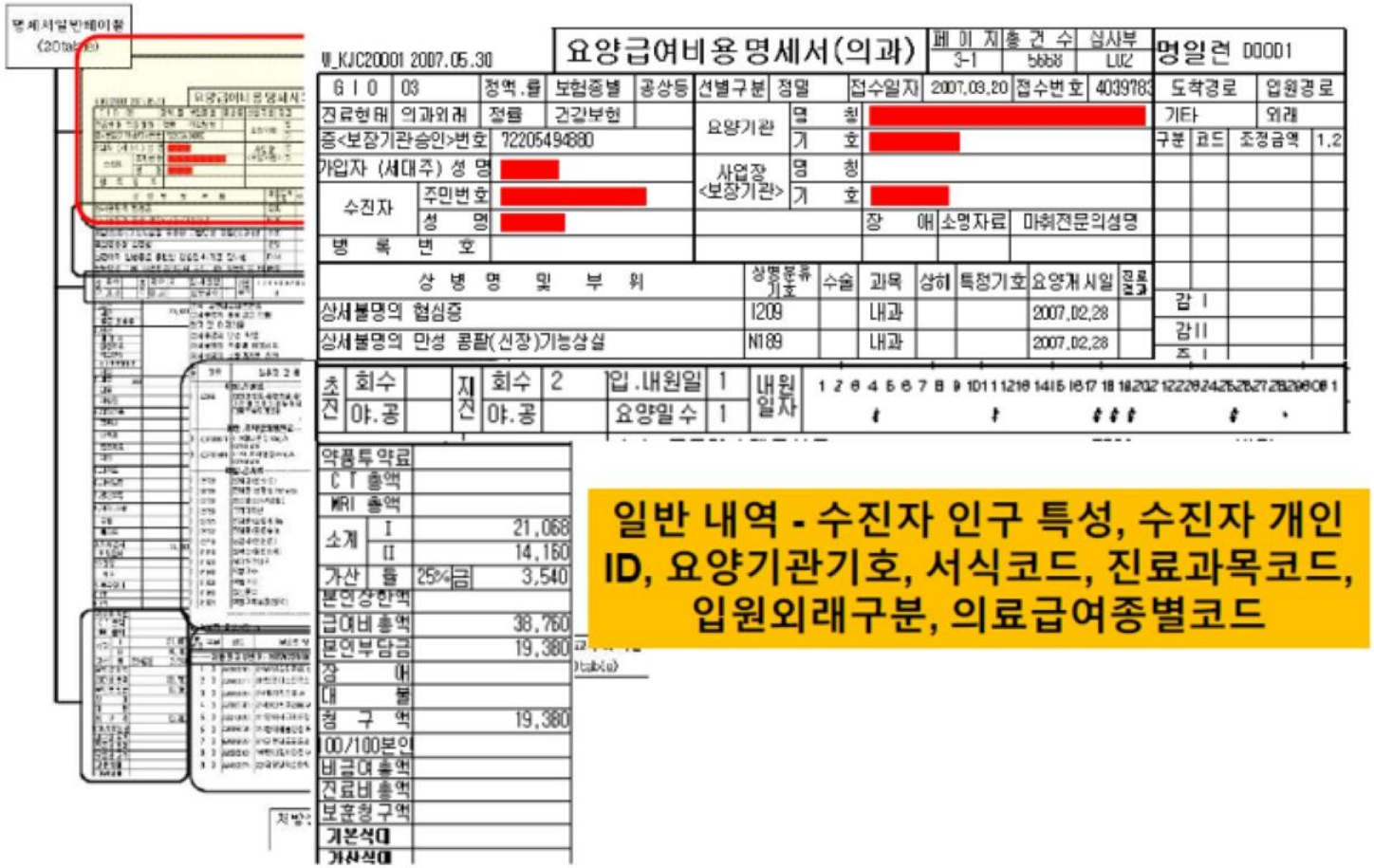
* 다양한 종류를 제공하고 있음.

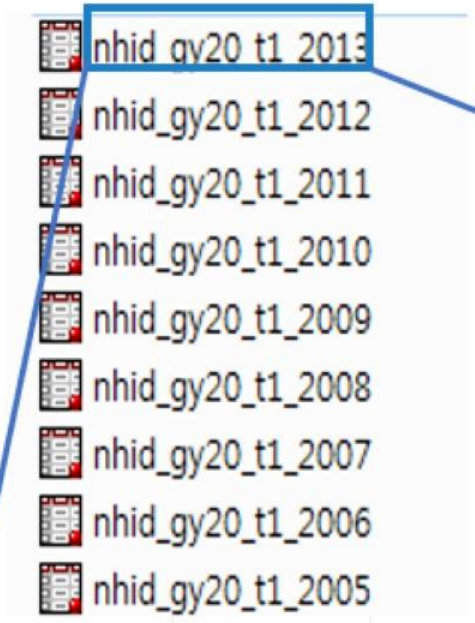
《 요양급여비용 청구명세서 구성 》



대상 자료	명세서 일반내역	상병내역	진료내역	의료기관 약 처방내역
자료 연계	명세서식별번호			
정보	- 성별 - 연령그룹 - 보험료분위 - 서식구분코드 (입원/외래구분코드) - 진료정보(요양개시/종료일자 등) - 주·부상병코드 - 급여비용	- 상병코드 - 상병분류유형코드 (주상병/부상병/배제상병)	- 원내행위내역 - 1회투약량 - 1일투약량 - 1일투여량 또는 실시횟수 - 총투여일수 또는 실시횟수 - 약품코드 - 주성분코드	- 1회투약량 - 1일투약량 - 총 투여일수 - 약품코드 - 주성분코드 - 약효분류번호

○ 명세서 일반 내역


요양급여비용 명세서(의과)
명일련 00001
일반 내역 - 수진자 인구 특성, 수진자 개인 ID, 요양기관기호, 서식코드, 진료과목코드, 입원외래구분, 의료급여종별코드

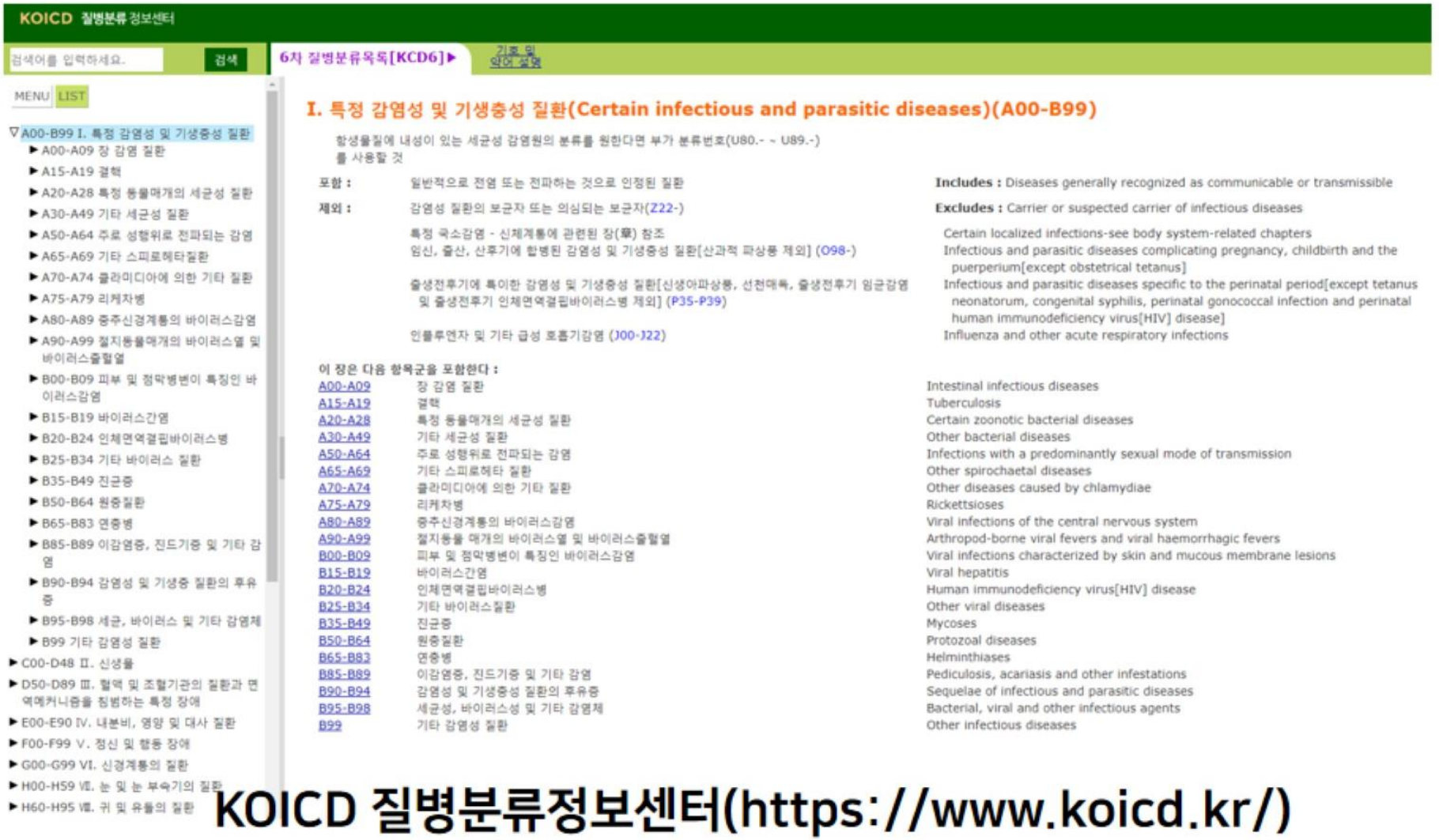


PERSON_ID	KEY_SEQ	YKIHO_ID	RECU_FR_DT	FORM_CD	DSBJT_CD	MAIN_SICK	SUB_SICK	IN_PAT_COURS_TYPE	
10000061	201301539904	124569	20131203	03	14	L298	L230		0
10000061	201301539905	124569	20131230	03	14	L298	L230		0
10000061	201301651081	179227	20131201	02	05	F009	S7290	32	0
10000061	201303421466	129106	20130102	08	00	I109			0
10000061	201307012639	129106	20130311	08	00	I109			0
10000061	201307275098	179159	20130323	03	04	S720			0

○ 명세서 일반 내역

- 서식코드 - 수진자가 요양기관에서 진료받은 진료형태
- 요양개시일자 - 요양급여비용명세서의 당월 요양 개시일 또는 내원일자 기재
- 주상병 - 진료기간 중 치료나 검사 등에 대한 환자의 요구가 가장 컸던 상병
  (한국표준질병사인분류표의 상병분류기호)

  EX) 혼수와 케토산증을 동반한 인슐린 의존 당뇨병



KOICD 질병분류정보센터(https://www.koicd.kr/)

3) 상병분류구분(SICK_DIV_TYPE_CD)

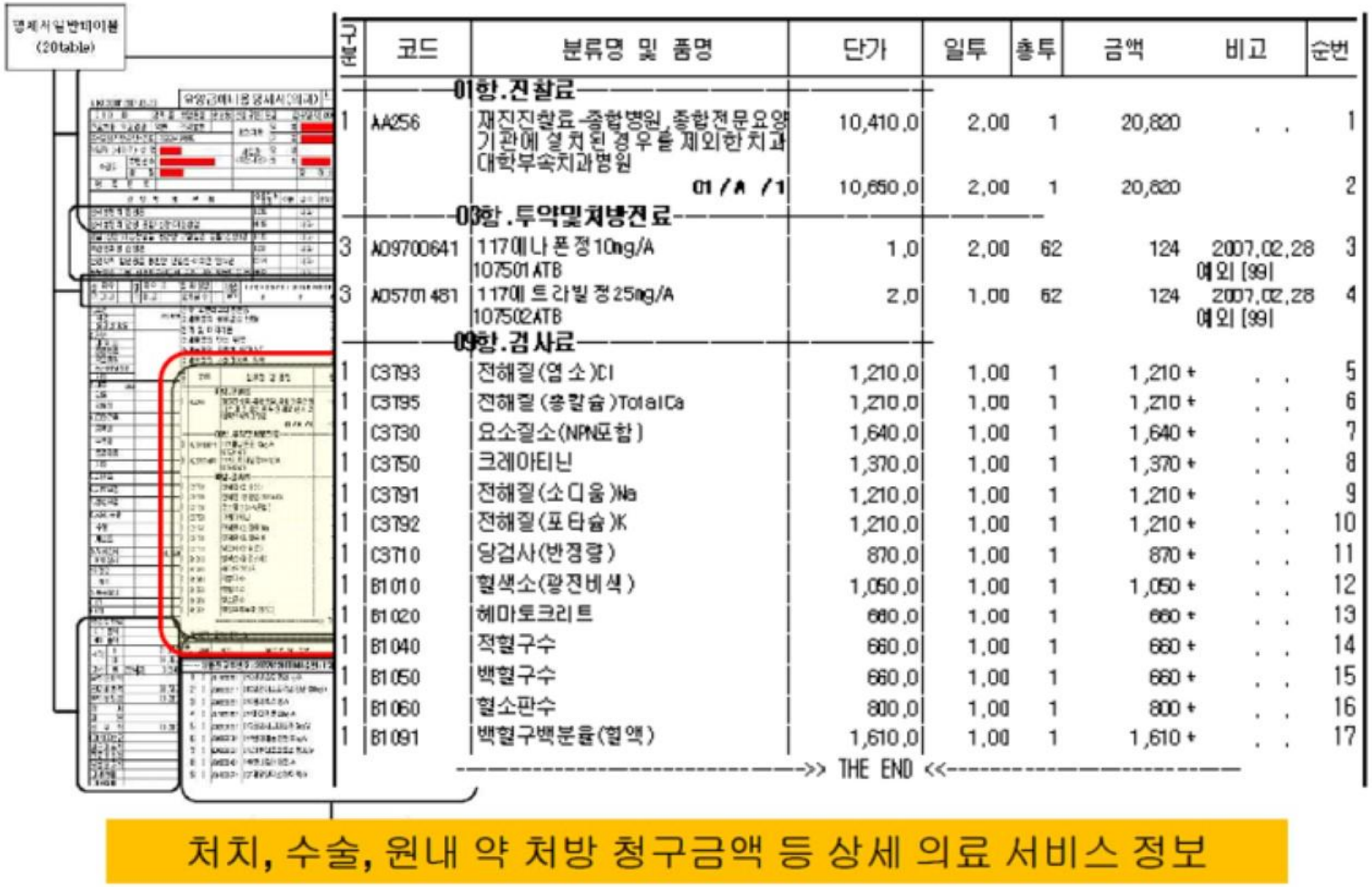
○ 각 상병분류기호별 주·부상병, 배제된 상병을 구분하는 구분자로서 상병분류기호별로 반드시 해당 구분자를 기재하고 있음

구분코드	해당항목	내용 (건강보험심사평가원 기재원칙)
1	주상병	진료기간 중 치료나 검사 등에 대한 환자의 요구가 가장 컸던 상병 ※ 상병분류기호' 첫번째 자리(제1단)의 상병에만 기재
2	부상병	진료기간 중 주상병과 함께 있었거나 발생된 상병으로 환자 진료에 영향을 주었던 상병
3	배제상병	최종상병이 확진된 경우 이전에 고려하였지만 배제된 상병

※ 상병분류구분 변수 값은 2004년부터 자료 존재함

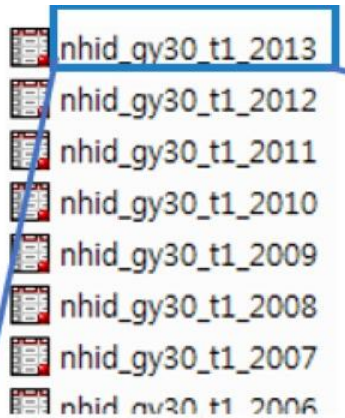
	의증	배제된 상병
의미	**의심가는 병**	**아니라고 제외된 병**
검사	가능	**가능**
처방/치료	가능	**하지 않음 (삭감 ??)**
전자차트에 표시	의증 으로 표시	배제된 상병 으로 표시
청구명세서 표시	**일반 진단명으로 청구**	**배제된 상병 으로 청구**

○ 진료내역



구분	코드	분류명 및 품명	단가	일투	총투	금액	비고	순번
		01항.진찰료						
1	AA256	재진진찰료-종합병원,종합전문요양기관에 설치된 경우를 제외한치과대학부속치과병원	10,410.0	2.00	1	20,820	. .	1
		01/A/1	10,650.0	2.00	1	20,820		2
		03항.투약및처방전료						
3	A09700641	117에나폰정10mg/A 107501ATB	1.0	2.00	62	124	2007.02.28 예외[99]	3
3	A05701481	117에트라빌정25mg/A 107502ATB	2.0	1.00	62	124	2007.02.28 예외[99]	4
		09항.검사료						
1	C3793	전해질(염소)Cl	1,210.0	1.00	1	1,210	. .	5
1	C3795	전해질(총칼슘)TotalCa	1,210.0	1.00	1	1,210	. .	6
1	C3730	요소질소(NPN포함)	1,640.0	1.00	1	1,640	. .	7
1	C3750	크레아티닌	1,370.0	1.00	1	1,370	. .	8
1	C3791	전해질(소디움)Na	1,210.0	1.00	1	1,210	. .	9
1	C3792	전해질(포타슘)K	1,210.0	1.00	1	1,210	. .	10
1	C3710	당검사(반정량)	870.0	1.00	1	870	. .	11
1	B1010	혈색소(광전비색)	1,050.0	1.00	1	1,050	. .	12
1	B1020	헤마토크리트	660.0	1.00	1	660	. .	13
1	B1040	적혈구수	660.0	1.00	1	660	. .	14
1	B1050	백혈구수	660.0	1.00	1	660	. .	15
1	B1060	혈소판수	800.0	1.00	1	800	. .	16
1	B1091	백혈구백분율(혈액)	1,610.0	1.00	1	1,610	. .	17
		>> THE END <<						

처치, 수술, 원내 약 처방 청구금액 등 상세 의료 서비스 정보



	KEY_SEQ	SEQ_NO	RECU_FR_DT	CLAUSE_CD	ITEM_CD	DIV_TYPE_CD	DIV_CD	I_II_TYPE	UN_COST	AMT
519	201301539898	2	20131206	01	02	1	AA254	1	9430	
520	201301539898	1	20131206	01	03	1	AH200	1	1700	
521	201301539899	2	20131205	01	02	1	AA254	1	9430	
522	201301539899	1	20131205	01	03	1	AH200	1	1700	
523	201301539900	1	20131230	01	01	1	AA154	1	13190	1
524	201301539901	1	20131219	01	01	1	AA154	1	13190	1
525	201301539902	1	20131227	01	02	1	AA254	1	9430	
526	201301539903	2	20131209	01	02	1	AA254	1	9430	
527	201301539903	1	20131209	03	03	3	654100070	1	2	
528	201301539904	1	20131203	01	02	1	AA254	1	9430	
529	201301539905	1	20131230	01	02	1	AA254	1	9430	
530	201301539906	2	20131217	03	03	3	654100070	1	2	
531	201301539906	1	20131217	01	02	1	AA254	1	9430	
532	201301539914	3	20131216	03	02	3	643800800	1	126	
533	201301539914	2	20131216	03	01	3	644305890	1	367	1
534	201301539914	1	20131216	03	01	3	641901440	1	43	
535	201301539915	5	20131223	03	01	3	642101080	1	55	
536	201301539915	4	20131223	03	01	3	642102570	1	15	

○ 진료 내역

- 항번호 및 목번호

항코드	설명	목코드	설명
01	진찰료	01	초진
		02	재진
		03	응급 및 회송료 등
		...	
S	특수장비	01	CT
		02	MRI
		03	PET

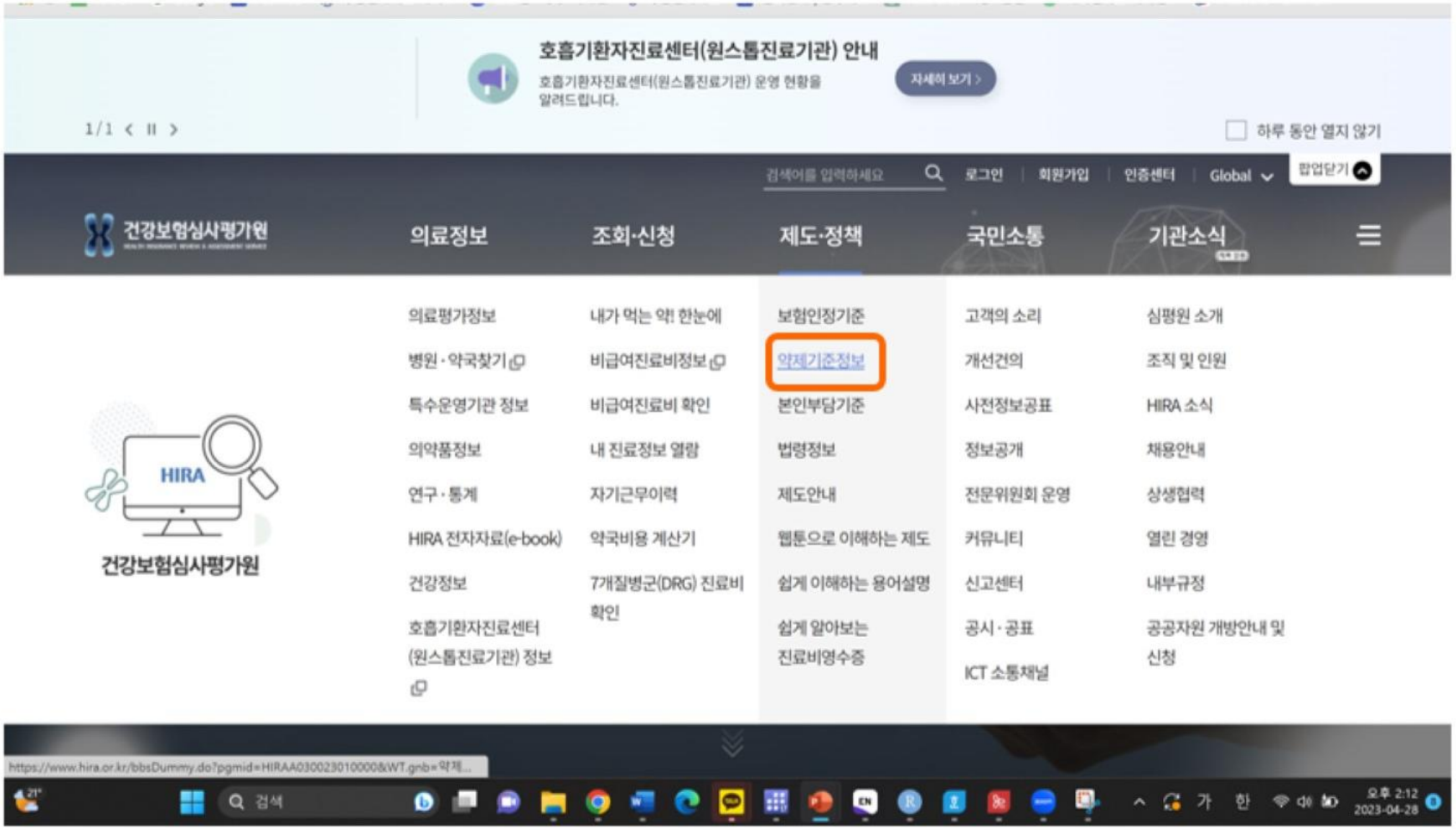
- 분류 코드 : 진료 내역에 해당하는 코드임.

  EX: 초진 진찰료

- 단가: 진료내역 분류코드 별 단가

약품 코드 조회: 건강보험심사평가원>통합검색>약제급여목록 및 급여 상한 금액 표로 검색

건강보험심사평가원 (https://www.hira.or.kr/)

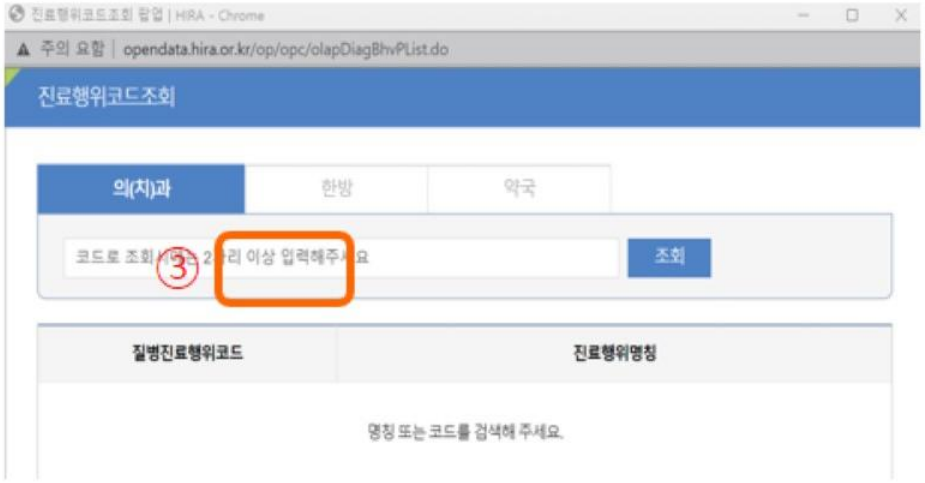


약품 코드 조회: 건강보험심사평가원>통합검색>약제급여목록 및 급여 상한 금액 표로 검색

건강보험심사평가원 (https://www.hira.or.kr/)

연번	투여	분류	주성분코드	제품코드	제품명	업체명	규격	단위	상한금액	전일	비고	목록정비 코드
1	내복	112	130830ASY	**chloral hydrate 9.5g(0.1g/mL)**								
2	내복	112	130830ASY	645302132	포크랄시럽(포수클로랄)_(9.5g/95mL)	한림제약(주)	95(1)	mL/병	129	전문		645302
3	내복	112	130832ASY	**chloral hydrate 1g(0.1g/mL)**								
4	내복	112	130832ASY	645302133	포크랄시럽(포수클로랄)_(1g/10mL)	한림제약(주)	10	mL/병	1,260	전문		
5	내복	112	130833ASY	**chloral hydrate 0.5g(0.1g/mL)**								
6	내복	112	130833ASY	645302135	포크랄시럽(포수클로랄)_(0.5g/5mL)	한림제약(주)	5	mL/병	847	전문		
7	내복	112	149203ATB	**doxepin hydrochloride (as doxepin 3mg)**								
8	내복	112	149203ATB	643507540	독세정3밀리그램(독세핀염산염)_(3.39mg/1정)	한미약품(주)	1	정	59	전문		
9	내복	112	149203ATB	651904420	명세핀정3밀리그램(독세핀염산염)_(3.39mg/1정)	명인제약(주)	1	정	96	전문		
10	내복	112	149203ATB	640006660	사일레노정3밀리그램(독세핀염산염)_(3.39mg/1정)	에이치케이이노엔(주)	1	정	97	전문		
11	내복	112	149203ATB	657806680	사일원정3밀리그램(독세핀염산염)_(3.39mg/1정)	하나제약(주)	1	정	97	전문		
12	내복	112	149204ATB	**doxepin hydrochloride (as doxepin 6mg)**								
13	내복	112	149204ATB	643507530	독세정6밀리그램(독세핀염산염)_(6.78mg/1정)	한미약품(주)	1	정	89	전문		
14	내복	112	149204ATB	649001610	리치나잇정6밀리그램(독세핀염산염)_(6.78mg/1정)	풍림무약(주)	1	정	89	전문		
15	내복	112	149204ATB	651904430	명세핀정6밀리그램(독세핀염산염)_(6.78mg/1정)	명인제약(주)	1	정	110	전문		
16	내복	112	149204ATB	640006770	사일레노정6밀리그램(독세핀염산염)_(6.78mg/1정)	에이치케이이노엔(주)	1	정	110	전문		
17	내복	112	149204ATB	657806690	사일원정6밀리그램(독세핀염산염)_(6.78mg/1정)	하나제약(주)	1	정	110	전문		
18	내복	112	160601ATB	**flunitrazepam 1mg**								
19	내복	112	160601ATB	651900330	루나팡정(플루니트라제팜)_(1mg/1정)	명인제약(주)	1	정	59	전문		
20	내복	112	160601ATB	657200130	라제팡정(플루니트라제팜)_(1mg/1정)	환인제약(주)	1	정	60	전문		
21	내복	112	161801ATB	**flurazepam hydrochloride 15mg**								
22	내복	112	161801ATB	642800250	달마론정(플루라제팜염산염)_(15mg/1정)	고려제약(주)	1	정	43	전문		
23	내복	112	211701ATB	**phenobarbital 30mg**								

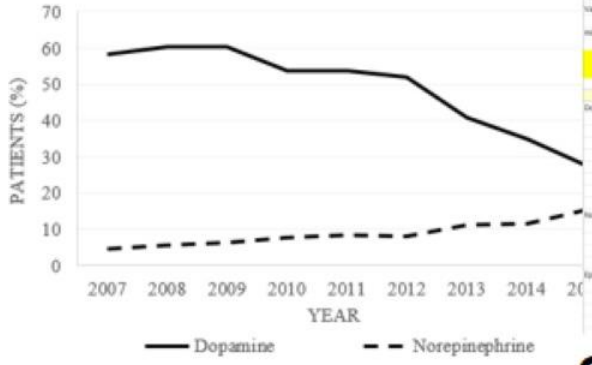
진료행위코드 조회: 보건의료빅데이터개방시스템(https://opendata.hira.or.kr/home.do)
의료통계정보>진료행위



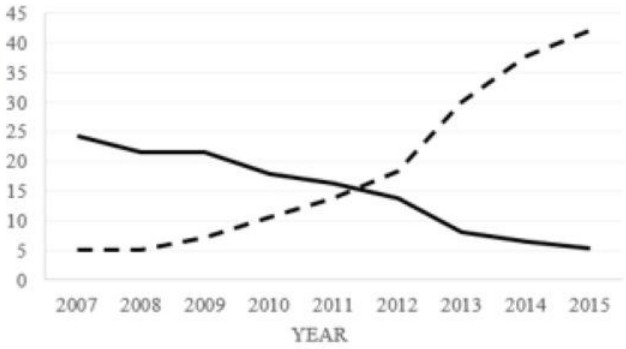
질병진료행위코드	진료행위명칭
AP502	외래 항암주사관리료-상급종합병원
AP503	항암요법 부작용 및 반응평가료-상급종합병원
AP602	외래 항암주사관리료-종합병원
AP603	항암요법 부작용 및 반응평가료-종합병원
AP702	외래 항암주사관리료-병원, 정신병원, 치과병원, 요양병원, 한방병원
AP703	항암요법 부작용 및 반응평가료-병원, 정신병원, 치과병원, 요양병원, 한방병원

○ Step 2: 주요 변수 생성

Figure 3. Previous version; Trend of single vasopressor pattern



gure 4. Newly version; Trend of single vasopressor pattern



연구 기간을 고려하여
삭제된 코드까지 확인 필요
(최근 코드만 확인?- NO!)

Supplement table 1. Previous version; odds ratio (95% confidence intervals) for i
mortality by type of vasopressor using mixed-effect logistic regression analysis

	Number of participants	Crude OR (95% CI)	
Single vasopressor			
Dopamine alone	26,117	Reference	
Norepinephrine alone	3,891	0.96 (0.87-1.04)	

*Adjusted for age, sex, year, insurance beneficiaries, cardiogenic, hypertension, diabetes mellitus, chronic kidney disease, charlson index, emergency room, add-on inotropes, ECMO, IABP, ICU quality grades and hospital region. (random-intercept of hostpial)

Dopamine Norepinephrine

; odds ratio (95% confidence intervals) for in-hospital
sing mixed-effect logistic regression analysis

	Number of participants	Crude OR (95% CI)	*Adjusted OR (95% CI)
	12,287	Reference	Reference
	16,514	1.33 (1.26-1.40)	1.23 (1.15-1.31)

*Adjusted for age, sex, year, insurance beneficiaries, cardiogenic, hypertension, diabetes mellitus, chronic kidney disease, charlson index, emergency room, add-on inotropes, ECMO, IABP, ICU quality grades and hospital region. (random-intercept of hostpial)

○ Step 2: 주요 변수 생성

상병, 입원 조합시의 유병률

<표 4-9> 5년간 간암 유병인구

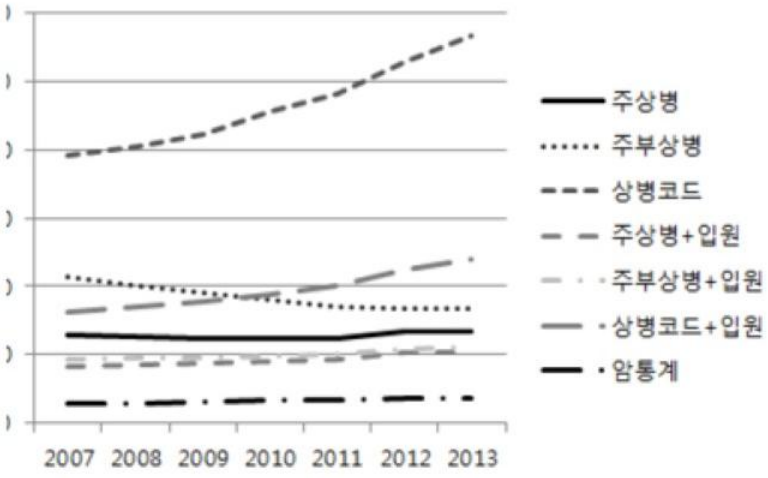
(단위 : 명)

연도	2007	2008	2009	2010	2011	2012	2013
통계청	27,447	29,204	30,852	32,508	34,602	35,804	36,890
주상병	2730	2649	2625	2583	2639	2761	2779
주부상병	4524	4216	4039	3761	3604	3496	3480
상병코드	8252	8502	8897	9448	10168	10941	11736
주상병+입원	1738	1782	1827	1874	1970	2115	2157
주부상병+입원	1960	1984	2019	2031	2116	2251	2301
상병코드+입원	3400	3583	3749	3891	4241	4643	4985

<표 4-10> 10만 명당 5년간 간암 유병인구

(단위 : 10만 명당)

연도	2007	2008	2009	2010	2011	2012	2013
통계청	55.9	59.1	62.1	65.2	69.1	71.1	73.0
주상병	259.3	251.8	249.4	248.6	249.6	266	268.3
주부상병	429.6	400.7	383.8	362	340.8	336.8	335.9
상병코드	783.7	808	845.3	909.5	961.5	1054.1	1132.9
주상병+입원	165.1	169.4	173.6	180.4	186.3	203.8	208.2
주부상병+입원	186.1	188.6	191.8	195.5	200.1	216.9	222.1
상병코드+입원	322.9	340.5	356.2	374.6	401	447.3	481.2



[그림 4-3] 조작적 정의별 연간 10만 명당 간암 유병인구 비교

병원

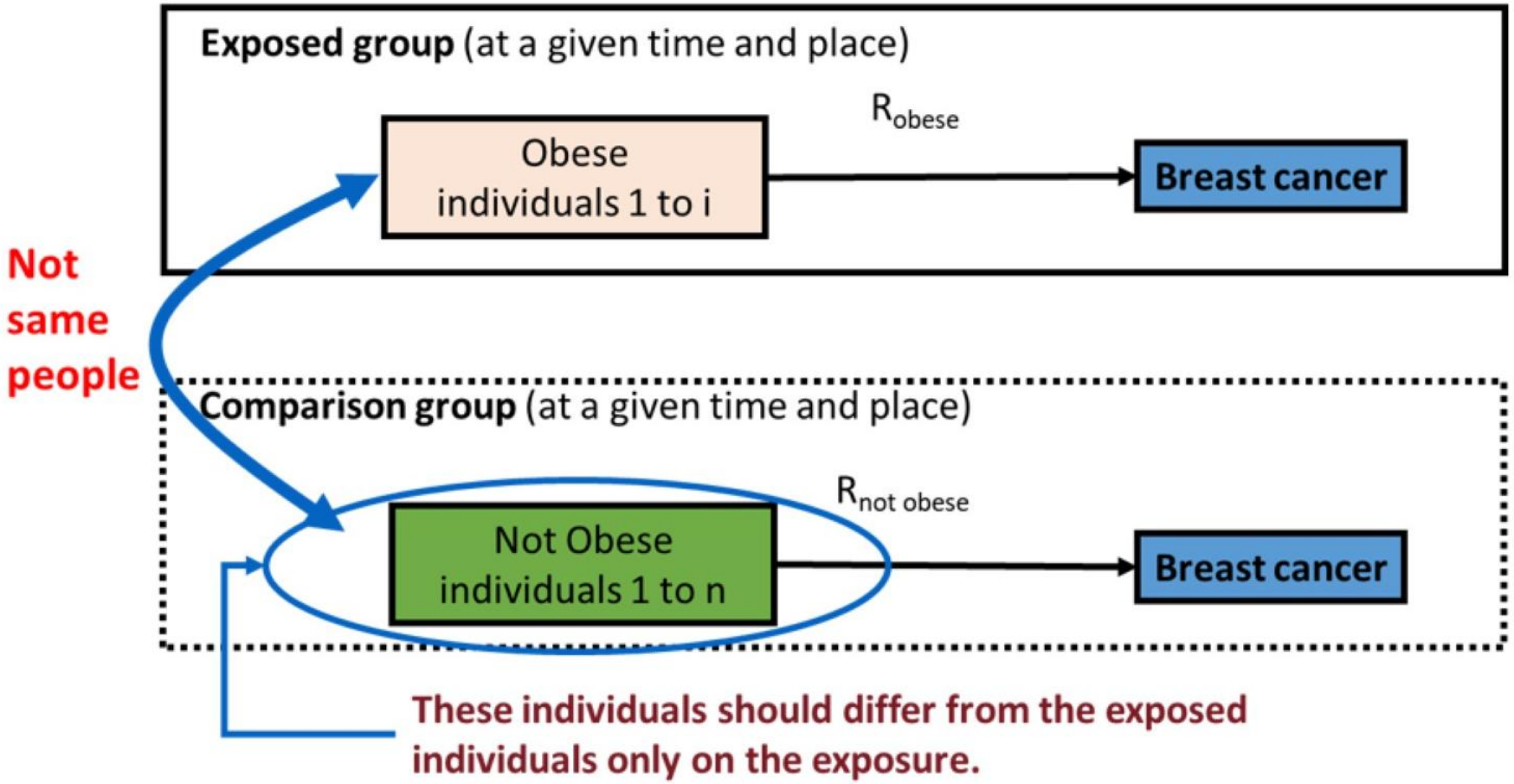
방문정보(20t)		상병정보(40t)
날짜	20130531	
진료과목	이비인후과	급성 편도염
주상병	급성편도염	급성 인후두염
부상병	급성인후두염	급성 화농성 중이염
요양일수	1일	급성 비인두염
서식	외과외래	급성 타액선염

청구요양급여비용총액	9430
청구본인부담금	2800
청구보험자부담금	6630

처방(30t, 60t)

약제	주성분	비고
알마겔정(알마게이트)(수출명:유한가스트라겔정)	almagate 500mg	보험등제약 (원외처방)
슈다페드정(수도에페드린염산염)	pseudoephedrine HCl 60mg	보험등제약 (원외처방)
코데닝정	chlorpheniramine maleate 1.5mg	보험등제약 (원외처방)
종근당아목시실린캡슐 500밀리그램	amoxicillin 500mg	보험등제약 (원외처방)
시네츄라시럽	dried coptidis rhizoma ext. (4.5~7:1) 0.875mg	보험등제약 (원외처방)
세토펜정325밀리그람(아세트아미노펜)	acetaminophen encapsulated(as acetaminophen) 325mg	보험등제약 (원외처방)
AA254	재진진찰료-의원,보건의료원내의과	수가 (원내처방)
총 처방일수	3일	

○ Step 4: 가설 검증 및 확인



3. 연구에 맞는 분석 하기
- 내 연구와 내 데이터에 맞는 방법으로 연구 수행하기!

1 조작적정의확인 (대상자특성 반드시 확인)

Lee et al. BMC Medicine (2018) 16:178
https://doi.org/10.1186/s12916-018-1159-7

BMC Medicine

RESEARCH ARTICLE Open Access

Racial differences in comorbidity profile among patients with chronic obstructive pulmonary disease

Hyun Lee[1], Sun Hye Shin[2], Seonhye Gu[3], Di Zhao[3], Danbee Kang[3,4], Yeong Rae Joi[3], Gee Young Suh[2], Roberto Pastor-Barriuso[6], Eliseo Guallar[4,5], Juhee Cho[3,4,5†] and Hye Yun Park[2*†]

Definitions

COPD was defined based on pre-bronchodilator FEV_1 / FVC < 0.7, and COPD severity was classified as mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$

Table 1 Characteristics of participants with COPD aged 40–79 by race and ethnicity, U.S. NHANES 2007–2012 and Korea NHANES 2007–2015[a]

	U.S. NHANES			Korea NHANES	
	Non-Hispanic White (n = 944)	Non-Hispanic Black (n = 324)	Hispanic[b] (n = 227)	Korean (n = 3808)	p value
Age, years	59.8(0.4)	59.6 (0.7)	59.6 (0.8)	63.6 (0.2)	< 0.001
Age group, years					< 0.001
40–49	18.7 (1.7)	20.7 (2.9)	19.7 (3.1)	11.3 (0.7)	
50–59	31.2 (2.2)	30.9 (2.6)	29.9 (3.9)	23.2 (0.9)	
60–69	30.3 (2.4)	24.1 (1.8)	32.0 (3.0)	31.2 (0.9)	
70–79	19.8 (1.3)	24.2 (2.5)	18.3 (2.7)	34.3 (1.0)	
Men, %	59.1 (2.4)	60.2 (2.3)	69.2 (4.2)	73.8 (0.9)	< 0.001
BMI, kg/m^2	27.7 (0.2)	27.8 (0.4)	28. 6 (0.4)	23.7 (0.1)	< 0.001
BMI group					0.023
Underweight	1.9 (0.5)	3.1 (1.2)	0	2.7 (0.4)	
Normal	32.3 (1.6)	35.1 (2.8)	27.4 (3.4)	38.9 (1.1)	
Overweight	37.8 (1.5)	33.4 (2.3)	41.9 (3.7)	27.6 (0.9)	
Obese	27.9 (1.4)	28.4 (2.6)	30.7 (3.8)	30.7 (1.0)	
					< 0.001
	33.5 (2.4)	42.4 (3.4)	26.4 (2.8)	41.6 (1.0)	
	39.9 (2.1)	26.4 (2.2)	35.5 (2.9)	27.9 (0.9)	
	26.6 (2.1)	31.3 (2.8)	38.1 (3.3)	30.5 (1.0)	

OPEN ACCESS

Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study

Hye Yun Park,[1] Danbee Kang,[2,3] Sun Hye Shin,[1] Kwang-Ha Yoo,[4] Gee Young Suh,[1] Hojoong Kim,[1] Young Mog Shim,[6] Eliseo Guall
O Jung Kwon[1]

For numbered affiliations see end of article.

Correspondence to
Dr Juhee Cho, Center for Clinical Epidemiology, Samsung Medical Center, Seoul 06351, South Korea; jcho@skku.edu

HYP and DK contributed equally. JC and OJK contributed equally.

Received 20 June 2019
Revised 25 November 2019
Accepted 31 December 2019
Published Online First
2 April 2020

ABSTRACT

There has been limited evidence for the association between chronic obstructive pulmonary disease (COPD) and the incidence of lung cancer among never smokers. We aimed to estimate the risk of lung cancer incidence in never smokers with COPD, and to compare it with the risk associated with smoking. This cohort study involved 338 548 subjects, 40 to 84 years of age with no history of lung cancer at baseline, enrolled in the National Health Insurance Service National Sample Cohort. During 2 355 005 person-years of follow-up (median follow-up 7.0 years), 1834 participants developed lung cancer. Compared with never smokers without COPD, the fully-adjusted smokers

Baseline characteristic	Overall (n=338 548)	COPD* No (n=326 169)	COPD* Yes (n=12 379)	P value
Sex				<0.001
Male	146 996 (43.4)	140 581 (43.1)	6415 (51.8)	
Female	191 552 (56.6)	184 588 (56.9)	5964 (48.2)	
Smoking status				<0.001
Never	241 633 (71.4)	233 266 (71.5)	8367 (67.6)	
Past	21 818 (6.4)	21 016 (6.4)	802 (6.5)	
Current	75 097 (22.2)	71 887 (22.0)	3210 (25.9)	

We included all men an
age, who underwent at
examination provided
study period (n=370
pants who had cancer
screening exam (basel
values for body mass i
the baseline exam (n=
size was 338 548 parti
191 552 women). The
of the Samsung Medical
and waived the requirement for informed consent as we used only de-identified data.

talisation with a C33 or C34 code.[8] COPD was defined as the presence of J43-J44 (except J43.0) codes and use of COPD medications at least twice within a year.[9] Smoking habits were measured by

Eligibility

- To emulate a hypothetical trial is fine.
- Design based on real-world practice

Supplement Table 1. Specification and emulation of a target trial evaluating the effect of NOAC versus warfarin on hazards of diabetes complications using real-world data from Taiwan's NHIRD

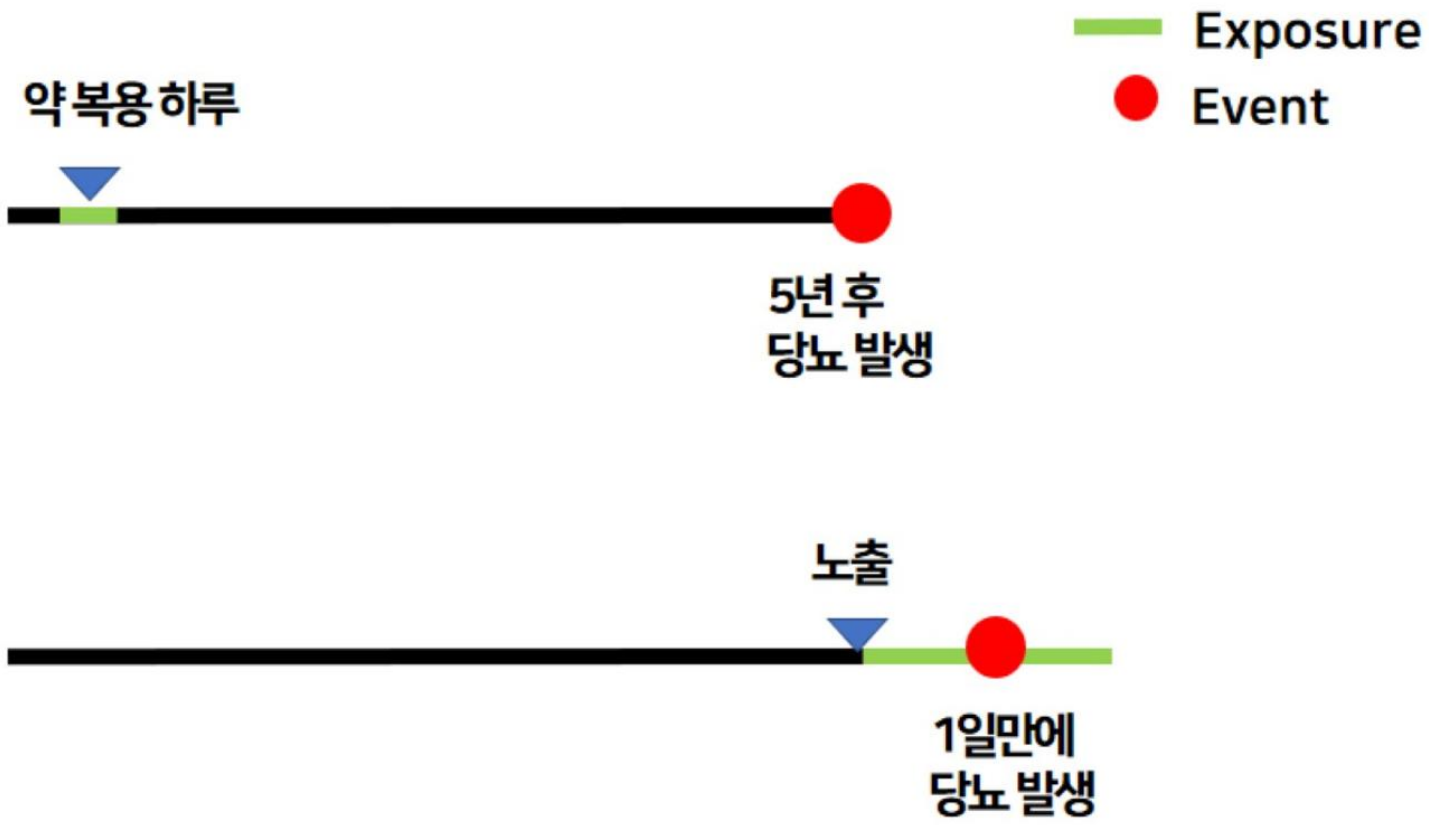
Component	Target trial	Emulated trial using real-world data
Eligibility	Adult patients aged ≥20 years previously diagnosed with AF and DM without severe valvular heart disease or end stage renal disease No prior use of oral anticoagulants.	Same, but with the exclusion of patients with a previous diagnosis of rheumatic heart disease, congenital heart disease, or who had received valve replacement surgery, because severe valvular heart disease is hard to define using diagnostic codes in NHIRD directly

Ann Intern Med.2022;175:490-498.

Eligibility criteria

- Met at a single time
- Met at multiple times
  - Choose one time (e.g., the first eligibility time or one time at random)
  - Use all eligibility times emulating multiple nested trials

1 조작적정의확인



빅데이터 분석 전 고려사항 : Exposure 와 Outcome 의 정의
상병 코드에 대한 확인

상황에 따라 삭감되는 경우 주의 필요 !!

3) 상병분류구분(SICK_DIV_TYPE_CD)

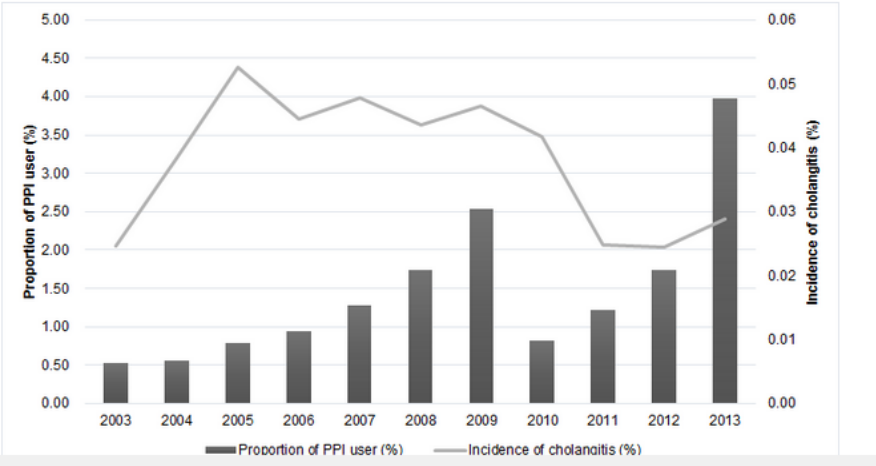
○ 각 상병분류기호별 주·부상병, 배제된 상병을 구분하는 구분자로서 상병분류기호별로 반드시 해당 구분자를 기재하고 있음

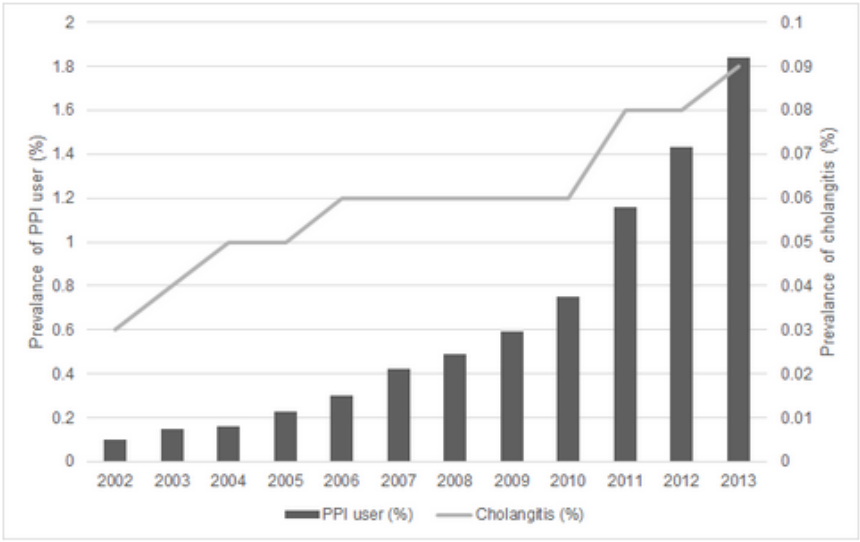
구분코드	해당항목	내용 (건강보험심사평가원 기재원칙)
1	주상병	진료기간 중 치료나 검사 등에 대한 환자의 요구가 가장 컸던 상병 ※ 상병분류기호' 첫번째 자리(제1단)의 상병에만 기재
2	부상병	진료기간 중 주상병과 함께 있었거나 발생된 상병으로 환자 진료에 영향을 주었던 상병
3	배제상병	최종상병이 확진된 경우 이전에 고려하였지만 배제된 상병

※ 상병분류구분 변수 값은 2004년부터 자료 존재함

빅데이터 분석 전 고려사항 : Exposure 와 Outcome 의 정의
시간에 따라 변화하는 상병/약제/재료 등의 코드 변경에 대한 고려

약도 2009년 까지 쭉 증가하다가, 2010년~2012년에 무슨일이 있는지모르겠는데 갑자기 뚝 떨어져서
혹시 이 사이에 어떤 약물 코드중에 빠진것이 있을까요?





빅데이터 분석 전 고려사항 : Exposure 와 Outcome 의 정의
시간에 따라 변화하는 진료 환경에 대한 고려

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Radiology

Use of Gadoxetic Acid–enhanced Liver MRI and Mortality in More than 30000 Patients with Hepatocellular Carcinoma: A Nationwide Analysis

Tae Wook Kang, MD • Sun-Young Kong, MD* • Danbee Kang, PhD • Min Woong Kang, MS • Young Kon Kim, MD • Seong Hyun Kim, MD • Dong Hyun Sinn, MD • Young Ae Kim, PhD • Kui Son Choi, PhD • Eun Sook Lee, MD • Sang Myung Woo, MD • Joung Hwan Back, PhD • Eliseo Guallar, DrPH • Juhee Cho, PhD*

From the Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea (T.W.K., Y.K.K., S.H.K.); Department of Cancer Biomedical Science, National Cancer Center Graduate School of Cancer Science and Policy, Goyang, South Korea (S.Y.K., E.S.L., S.M.W.); Department of Laboratory Medicine, Hospital, National Cancer Center, Goyang, South Korea (S.Y.K.); Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, South Korea (D.K., E.G., J.C.); Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (D.K., M.W.K., E.G., J.C.); Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (D.H.S.); National Cancer Control Institute, National Cancer Center, Goyang, South Korea (Y.A.K., K.S.C.); Department of Cancer Control and Population Health, National Cancer Center Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, South Korea (K.S.C.); Center for Breast Cancer, Hospital, National Cancer Center, Goyang, South Korea (E.S.L.); Center for Liver Cancer, Hospital, National Cancer Center, Goyang, South Korea (S.M.W.); Health Insurance Policy Research Institute, National Health Insurance Service, Wonju, South Korea (J.H.B.); and Department of Epidemiology, and Welch Center for Epidemiology, Prevention, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, 2024 E Monument St, Baltimore, MD 21205 (E.G., J.C.). Received March 20, 2019; revision requested May 21; revision received November 15; accepted November 26. **Address correspondence to** J.C. (e-mail: *jcho@skku.edu*).

Materials and Methods

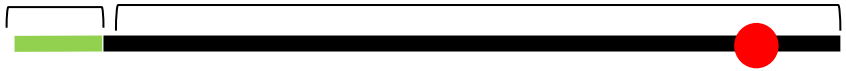
Study Population and Design

The institutional review board of the National Cancer Center approved this retrospective study and waived the requirement for informed consent because of the retrospective nature of our study, which used deidentified data. We conducted a retrospective nationwide cohort analysis of all patients aged 18–80 years with HCC (International Classification of Diseases, 10th Revision [ICD-10] code C22.0) in South Korea without a history of cancer and who had undergone CT with or without MRI as part of their diagnostic work-up. HCC cases were identified from the Korea National Cancer Incidence Database, a nationwide hospital-based cancer registry that has collected information from all cancer cases in Korea since 1999 (17). We restricted our analysis to patients with HCC diagnosed from January 1, 2008, to December 31, 2010 (n = 31 120). We selected this timeframe because the Korea NHIS started to cover the use of gadoxetic acid (Primovist or Eovist; Bayer Schering Pharma, Berlin, Germany) as a contrast material for dynamic MRI in May 2007, and, after 2010, the addition of gadoxetic acid–enhanced MRI to multiphase CT became a common diagnostic work-up test for patients with HCC (18).

빅데이터 분석 전 고려사항 : Exposure 와 Outcome 의 정의 상황에 대한 고려

- Exposure 되었다는 정의?
  - 최소 노출기간?

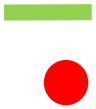
약물 복용 (1일)



예) 1일 복용으로 인하여 event 가 일어났다고 보기 어려움
▶최소 "일정 기간 노출"한 것만 exposure 로 정의

Exposure

Event



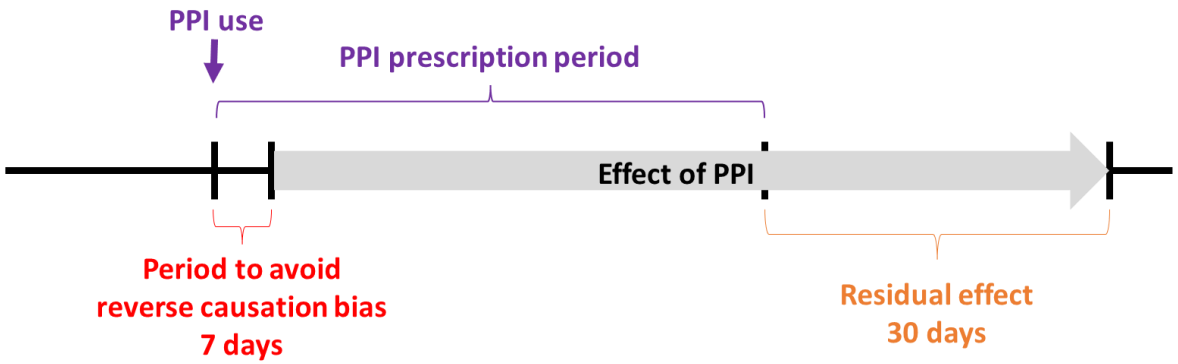
Received: 19 March 2019 | First decision: 9 April 2019 | Accepted: 28 July 2019
DOI: 10.1111/apt.15466
APT Alimentary Pharmacology & Therapeutics WILEY

Use of proton pump inhibitors and the risk of cholangitis: a nationwide cohort study

Yang Won Min[1] | Danbee Kang[2,3] | Ju-Young Shin[4] | Minwoong Kang[3] | Joo Kyung Park[1] | Kwang Hyuck Lee[1] | Jong Kyun Lee[1] | Kyu Taek Lee[1] | Poong-Lyul Rhee[1] | Jae J. Kim[1] | Eliseo Guallar[3,5] | Juhee Cho[2,3,5] | Hyuk Lee[1]

2.3 | Definition of PPI exposure

PPI use was identified in prescriptions with Korean Drug and Anatomical Therapeutic Chemical Codes A02BC01, A02BC02, A02BC03, A02BC04, A02BC05. PPI use was considered as a time-varying variable to control immortal time bias.[24,25] To avoid reverse causation bias due to the possible prescription of PPIs for symptoms caused by cholangitis, we considered that PPI use could not be responsible for cases of cholangitis occurring in the first 7 days after initiating PPI treatment. Also, as the effects of PPI on the microbiome may persist after medication use has ended, for each PPI prescription, we considered that the patient continued to be potentially affected by the effects of PPIs until 30 days after the date of expiration of the prescription (ie, we assumed that the effect of PPIs had a residual effect that persisted for 30 days after using the medication). If a new prescription was redeemed <30 days after the expiration of a prior prescription, the gap was considered as an ex-



2 인과관계확인

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Radiolo

Use of Gadoxetic Acid–enhanced Liver MRI and Mortali in More than 30000 Patients with Hepatocellular Carcinoma: A Nationwide Analysis

Tae Wook Kang, MD • Sun-Young Kong, MD* • Datshee Kang, PhD • Min Woong Kang, MS • Young Kon Kim, MD • Seong Hyun Kim, MD • Dong Hyun Sinn, MD • Young Ae Kim, PhD • Kui Son Choi, PhD • Eun Sook Lee, MD • Sang Myung Woo, MD • Joong Hwan Baek, PhD • Eliseo Guallar, DrPH • Jubee Cho, PhD*

From the Department of Radiology and Center for Imaging Science, Samsung Medical Center, Sungkyunkwan University, Seoul, South Korea (T.W.K., Y.K.K., S.I
Department of Cancer Biomedical Science, National Cancer Center Graduate School of Cancer Science and Policy, Goyang, South Korea (S.Y.K., E.S.L., S.M.W.
partment of Laboratory Medicine, Hospital, National Cancer Center, Goyang, South Korea (S.Y.K.); Department of Clinical Research Design and Evaluation, SA
Sunglyunkwan University, Seoul, South Korea (D.K., E.G., J.C.); Center for Clinical Epidemiology, Samsung Medical Center, Sungkyunkwan University Sch
Medicine, Seoul, South Korea (D.K., M.W.K., E.G., J.C.); Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine,
South Korea (D.H.S.); National Cancer Control Institute, National Cancer Center, Goyang, South Korea (Y.A.K., K.S.C.); Department of Cancer Control and P
tion Health, National Cancer Center Graduate School of Cancer Science and Policy, National Cancer Center, Goyang, South Korea (K.S.C.); Center for Breast C
Hospital, National Cancer Center, Goyang, South Korea (E.S.L.); Center for Liver Cancer, Hospital, National Cancer Center, Goyang, South Korea (S.M.W.);
Insurance Policy Research Institute, National Health Insurance Service, Wonju, South Korea (J.H.B.); and Department of Epidemiology, and Welch Center for Epid
egy, Prevention, and Clinical Research, Johns Hopkins Bloomberg School of Public Health, 2024 E Monument St, Baltimore, MD 21205 (E.G., J.C.). Received
20, 2019; revision requested May 21; revision received November 15; accepted November 26. **Address correspondence to** J.C. (e-mail: *jcho@jhu.edu*).

Materials and Methods

Study Population and Design

The institutional review board of the National Cancer Center approved this retrospective study and waived the requirement for informed consent because of the retrospective nature of our study, which used deidentified data. We conducted a retrospective nationwide cohort analysis of all patients aged 18–80 years with HCC (International Classification of Diseases, 10th Revision [ICD-10] code C22.0) in South Korea without a history of cancer and who had undergone CT with or without MRI as part of their diagnostic work-up. HCC cases were identified from the Korea National Cancer Incidence Database, a nationwide hospital-based cancer registry that has collected information from all cancer cases in Korea since 1999 (17). We restricted our analysis to patients with HCC diagnosed from January 1, 2008, to December 31, 2010 (n = 31 120). We selected this timeframe because the Korea NHIS started to cover the use of gadoxetic acid (Primovist or Eovist; Bayer Schering Pharma, Berlin, Germany) as a contrast material for dynamic MRI in May 2007, and, after 2010, the addition of gadoxetic acid–enhanced MRI to multiphase CT became a common diagnostic work-up test for patients with HCC (18).

2 인과관계확인

Association Between Regular Moderate to Vigorous Physical Activity Initiation Following COPD Diagnosis and Mortality

An Emulated Target Trial Using Nationwide Cohort Data

Taeyun Kim, MD; Hyunsoo Kim, MS; Sunga Kong, PhD; Sun Hye Shin, MD, PhD; Juhee Cho, PhD; Danbee Kang, PhD; and Hye Yun Park, MD, PhD

BACKGROUND: Moderate to vigorous physical activity (MVPA) in patients with COPD affects their overall health outcomes, including symptom relief and improved quality of life. However, the magnitude of the effect of MVPA initiation on real-world clinical outcomes has not been well investigated.

RESEARCH QUESTION: How does MVPA initiation affect mortality and severe exacerbation in patients who have not engaged in MVPA prior to COPD diagnosis?

STUDY DESIGN AND METHODS: This study included patients with COPD aged ≥ 40 years who were not performing MVPA prior to COPD diagnosis and who had at least one health screening visit prior to and following their COPD diagnosis between January 1, 2010, and December 31, 2018. The main exposure was MVPA, defined as vigorous aerobic exercise > 20 min per day on ≥ 3 days per week or moderate aerobic exercise > 30 min per day on ≥ 5 days per week. The primary end point was all-cause mortality, and the secondary end point was initial severe exacerbation as the time to event following COPD diagnosis.

RESULTS: In total, 110,097 person-trials were included (27,564 MVPA increases and 82,533 control groups). No differences were observed between the covariates following matching. The adjusted hazards ratio of all-cause mortality for the MVPA group compared with the control group was 0.84 (95% CI, 0.79-0.89). In the subgroup analysis, patients aged > 65 years, female patients, those who had never smoked, and patients with a higher Charlson Comorbidity Index score displayed a stronger effect of MVPA on reducing mortality than younger male patients, those who had ever smoked, and patients with a lower Charlson Comorbidity Index score ($P_{interaction} < .05$). The fully adjusted hazards ratio for the risk of severe exacerbation (MVPA group vs control) was 0.90 (95% CI, 0.87-0.94).

INTERPRETATION: Initiation of MVPA can potentially reduce mortality and severe exacerbations in patients with COPD, although personalized interventions and further clinical trials are necessary.

CHEST 2024; 165(1):84-94

KEY WORDS: COPD; exacerbation; mortality; physical activity

ABBREVIATIONS: CCI = Charlson Comorbidity Index; HR = hazard ratio; ICD-10 = International Classification of Diseases, Tenth Revision; ICS = inhaled corticosteroids; K-NHIS = Korean National Health Insurance System; MVPA = moderate to vigorous physical activity; PA = physical activity; SMD = standardized mean difference

AFFILIATIONS: From the Division of Pulmonary and Critical Care Medicine (T. K., S. H. S., and H. Y. P.), Department of Internal Medicine, Samsung Medical Center, and Department of Clinical Research Design and Evaluation (J. C. and D. K.), SAIHST, Sungkyunkwan University, Seoul, South Korea; and Center for Clinical Epidemiology (H. K., S. K., J. C., and D. K.) and Patient-Centered Outcomes Research Institute (S. K.), Samsung Medical Center, Seoul, South Korea.

Drs T. Kim and H. Kim contributed equally to this article.

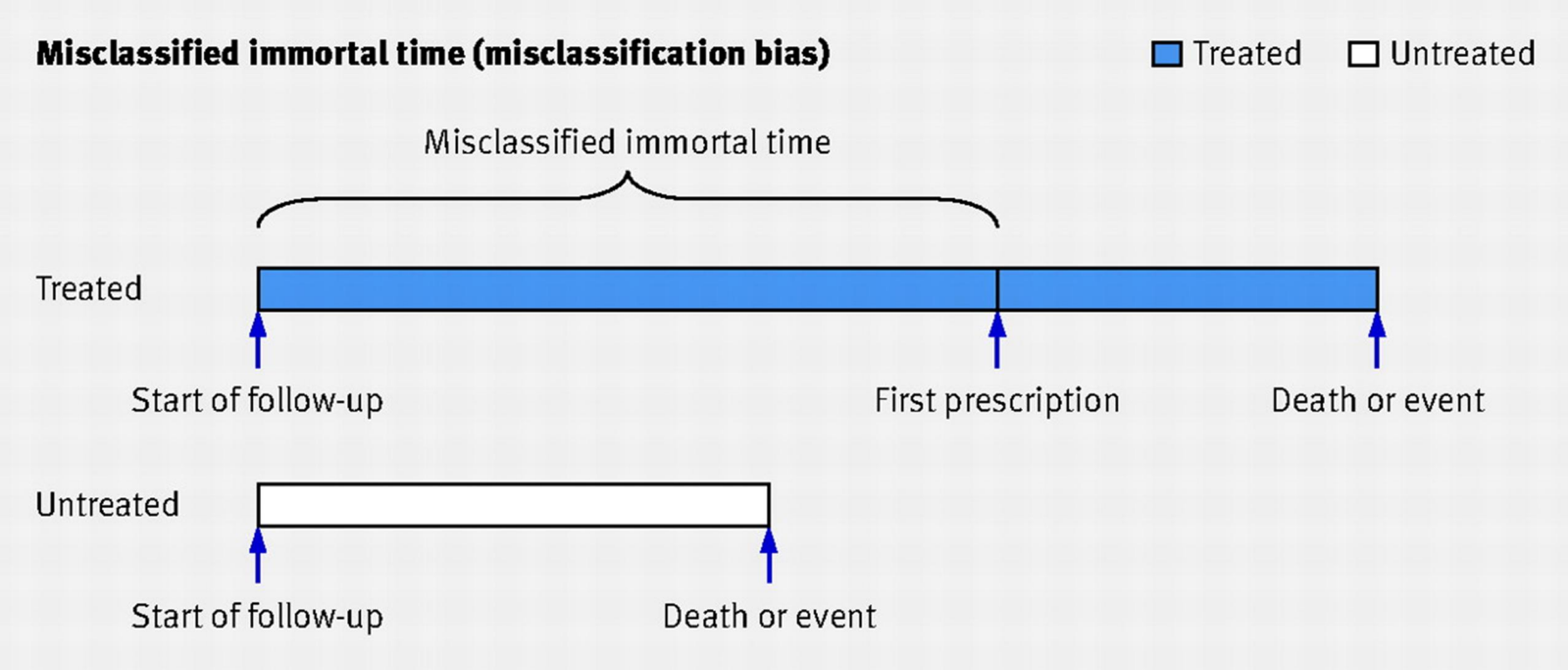
Drs Kang and Park contributed equally to this article.

CORRESPONDENCE TO: Hye Yun Park, MD, PhD; email: hyeyunpark@skku.edu

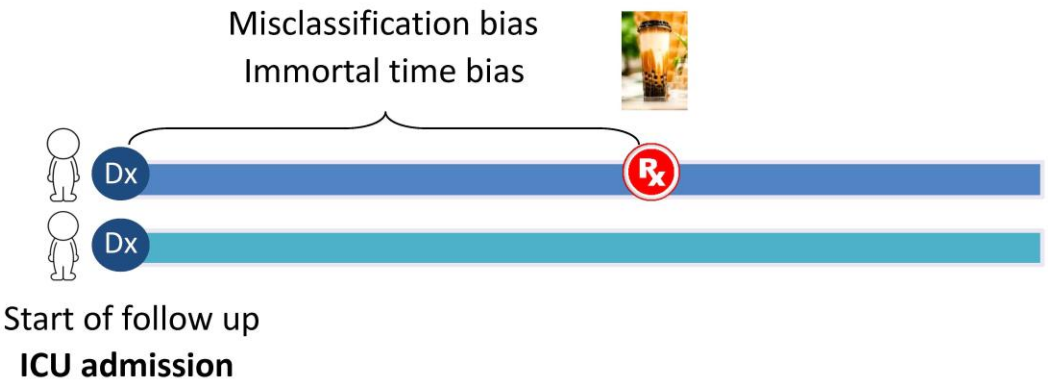
DOI: https://doi.org/10.1016/j.chest.2023.07.017

of 4 years for the health screening examinations. Among eligible patients, to minimize potential reverse causality, participants with a history of cancer (ICD-10 code C) were excluded. Furthermore, to minimize potential reverse causality, participants were excluded who developed cancer (ICD-10 code C) or died within 6 months of the health screening examination.

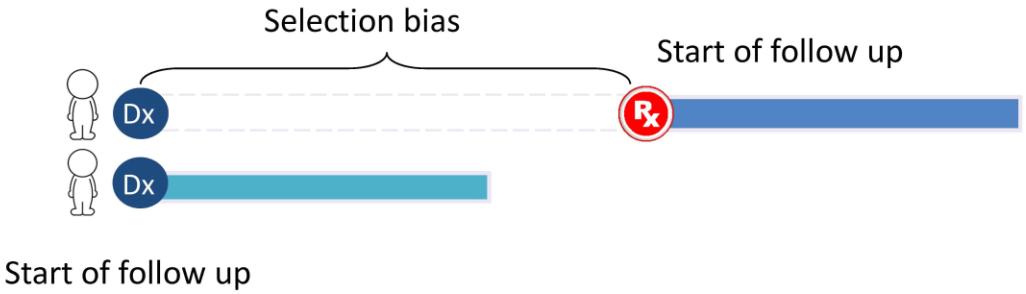
2 인과관계확인


Misclassified immortal time (misclassification bias)
Treated
Untreated
Misclassified immortal time
Treated
Start of follow-up
First prescription
Death or event
Untreated
Start of follow-up
Death or event

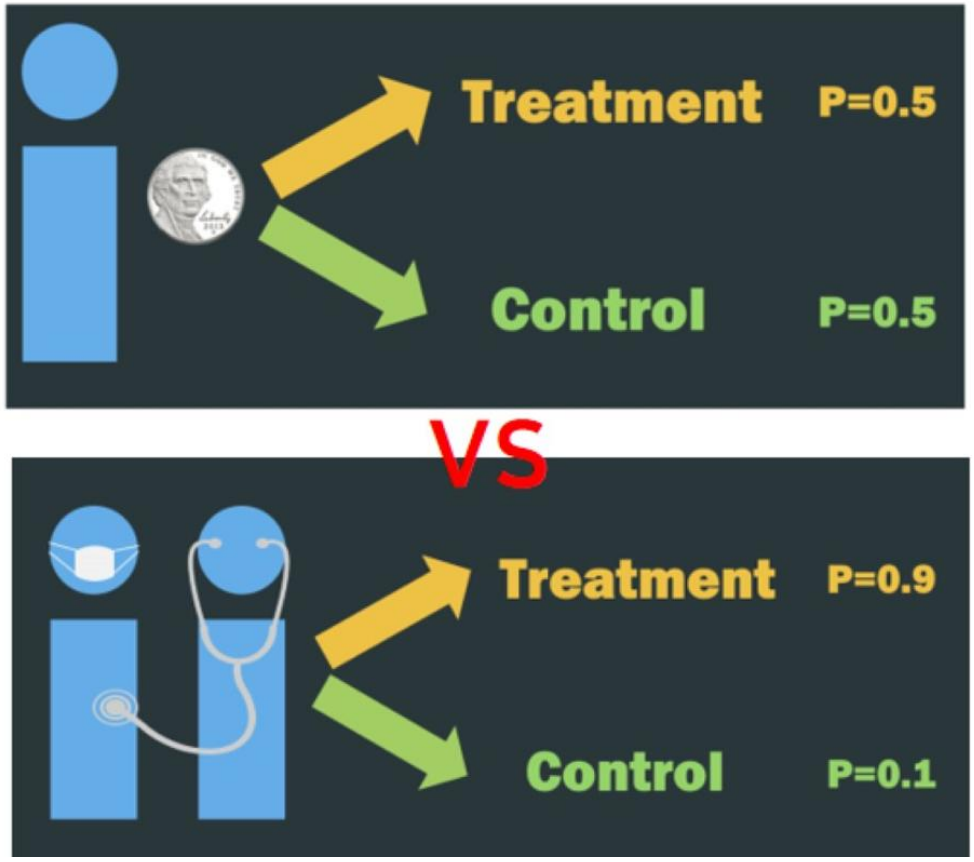
2 인과관계확인



	# of subjects	# of Death	Person-year	Rate (per-100 person year)	RR (95%CIs)
Non-bubble tea	771	148	674.6	21.9	Reference
Bubble tea	771	114	713.0	16.0	0.73 (0.57-0.93)
Day 0 - day3	771	0	**102.4**		
After day3	771	114	610.6		

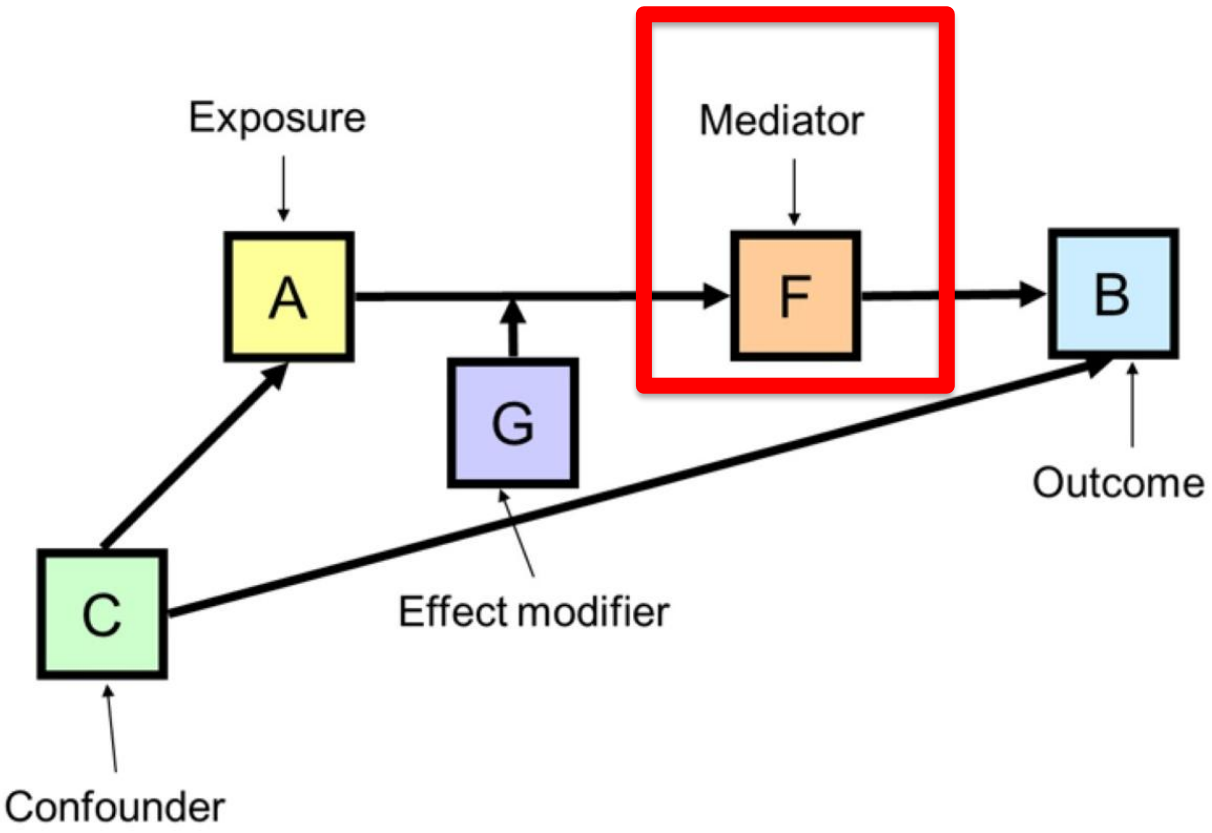


	# of subjects	# of Death	Person-year	Rate (per-100 person year)	RR (95%CIs)
Non-bubble tea	771	148	674.6	21.9	Reference
Bubble tea	771	114	610.6	18.7	0.82 (0.66-0.98)


Treatment
P=0.5
Control
P=0.5
VS
Treatment
P=0.9
Control
P=0.1

우리의 오해

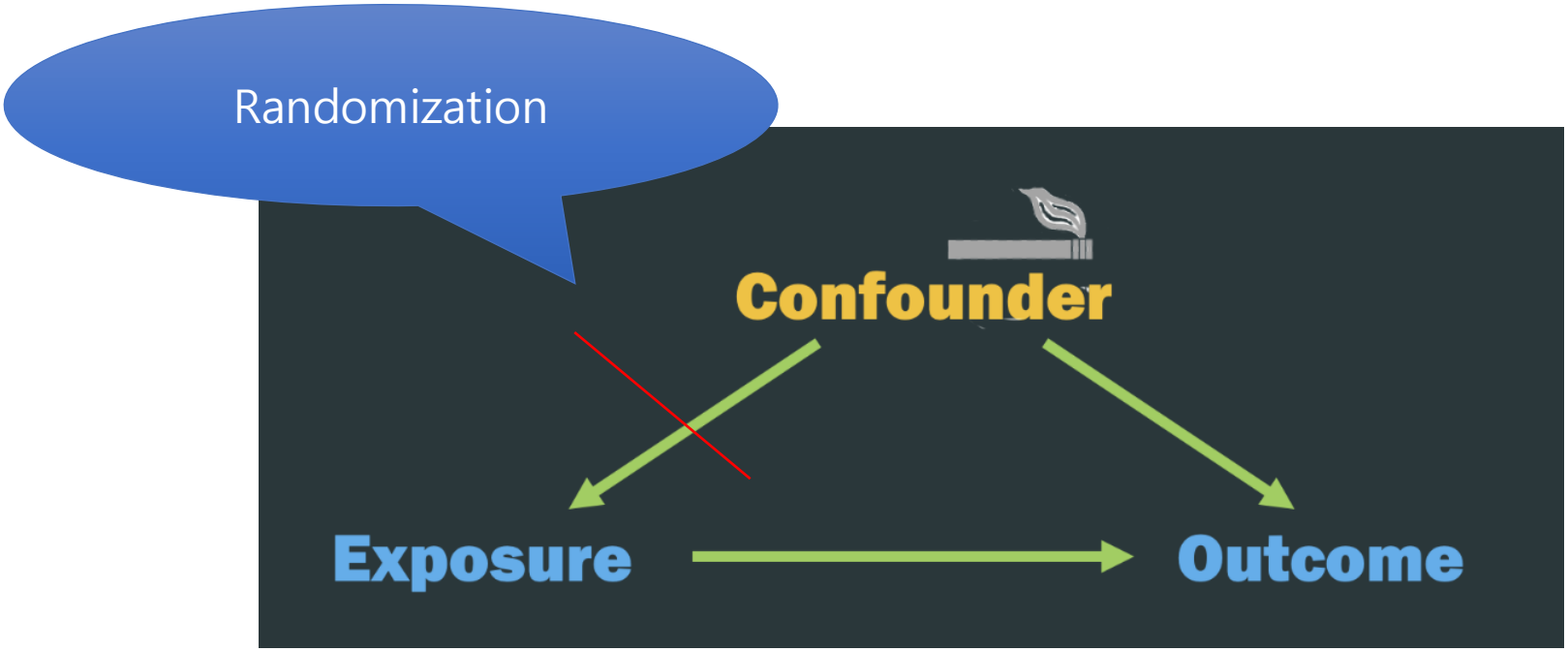
“있는 변수들 싹~ 다 보정하면 되지 않나요?”


Exposure
Mediator
A
F
B
G
Outcome
C
Effect modifier
Confounder

Mediator

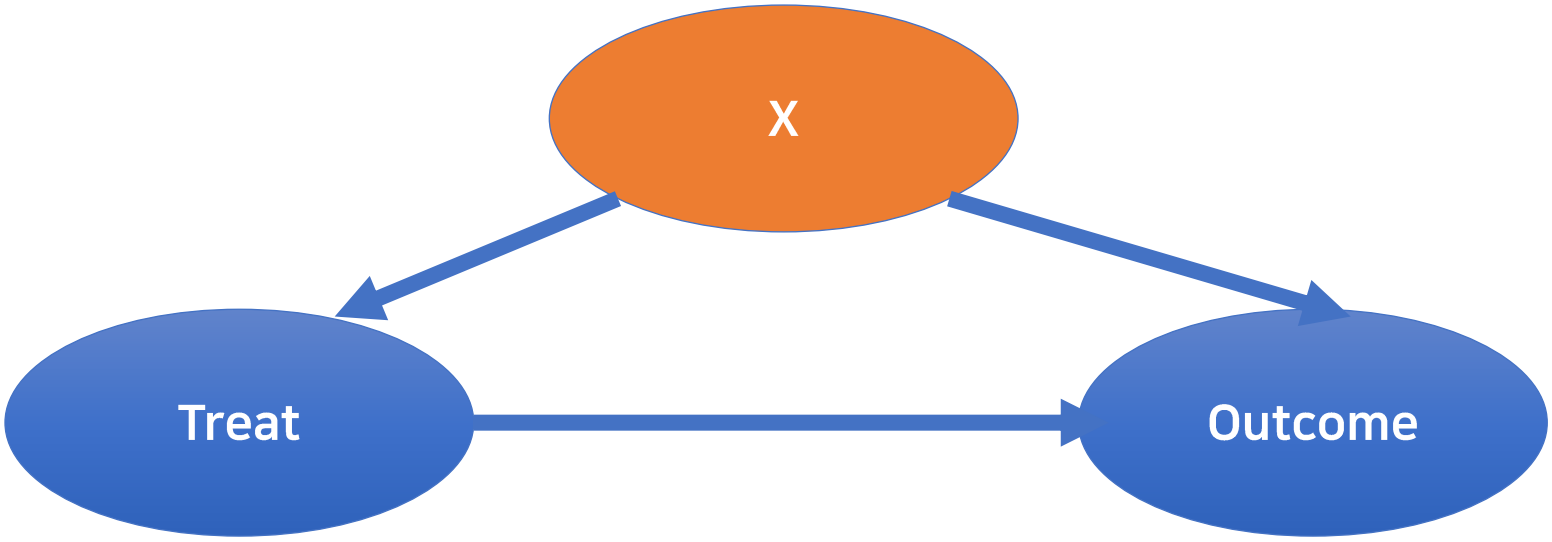
We are interested in the effect of smoking (exposure) on cancer (outcome)

- Smoking has a direct and an indirect effect on cancer
- Inflammation is a mediator (mediates part of the effect of smoking on cancer)
- If adjusting for (conditioning on) inflammation:
  - Total effect of s mated

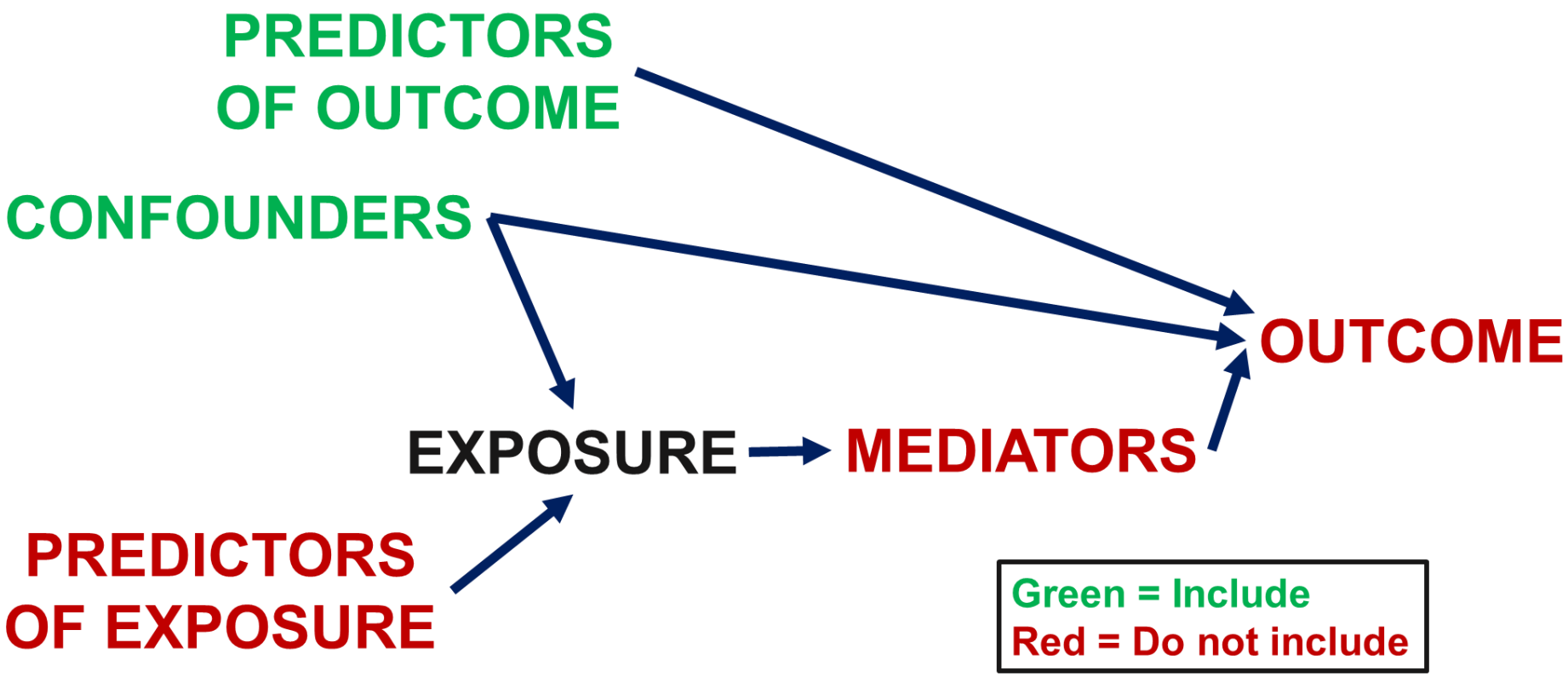

Randomization
Confounder
Exposure
Outcome

Propensity Score Matching

- Confounder 를 모두 포함
  - 결과변수와 treatment 변수에 영향을 주는 가능한 모든 변수를 포함 (confounder 를 모두 포함)



Propensity Score Matching



Clinical Review & Education

JAMA Guide to Statistics and Methods

Target Trial Emulation
A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH; Wei Wang, PhD; David E. Leaf, MD, MMSc

Quantifying the effect of a treatment on a clinical outcome—causal inference—requires the comparison of outcomes under different courses of action. For example, to quantify the effect of tocilizumab on mortality in critically ill patients with COVID-19, the mortality risk could be compared between a group of patients administered tocilizumab and a group who are not. Ideally, eligible patients would be assigned to these groups at random. The key advantage of such a randomized trial is that both groups are expected to be comparable, and thus any differences in mortality can be attributed to tocilizumab rather than to prognostic differences between the groups.

being administered tocilizumab could be considered a potential member of either treatment group. To avoid immortal time bias[3] and ensure time zero is considered correctly, such a patient may be "cloned" and, until 2 days have passed or tocilizumab is started, be represented in both treatment groups.[4]

Why Is Target Trial Emulation Used in the Analysis of Observational Data?

The goal of target trial emulation is to avoid making fundamental errors that can result in erroneous causal conclusions. For example, a randomized trial found an increased risk of coronary heart disease

JAMA. 2022;328(24):2446-2447.

Check for updates

1 Unit of Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

2 Department of Global Health and Population and Department of Epidemiology, Harvard T H Chan School of Public Health, Harvard University, Boston, MA, USA

3 Oxford Population Health, Big Data Institute, University of Oxford, Oxford, UK

4 Faculty of Medicine, University of Southampton, Southampton, UK

5 Institute of Public Health, Charité–Universitätsmedizin Berlin, Berlin, Germany

FAST FACTS

Target trial emulation: applying principles of randomised trials to observational studies

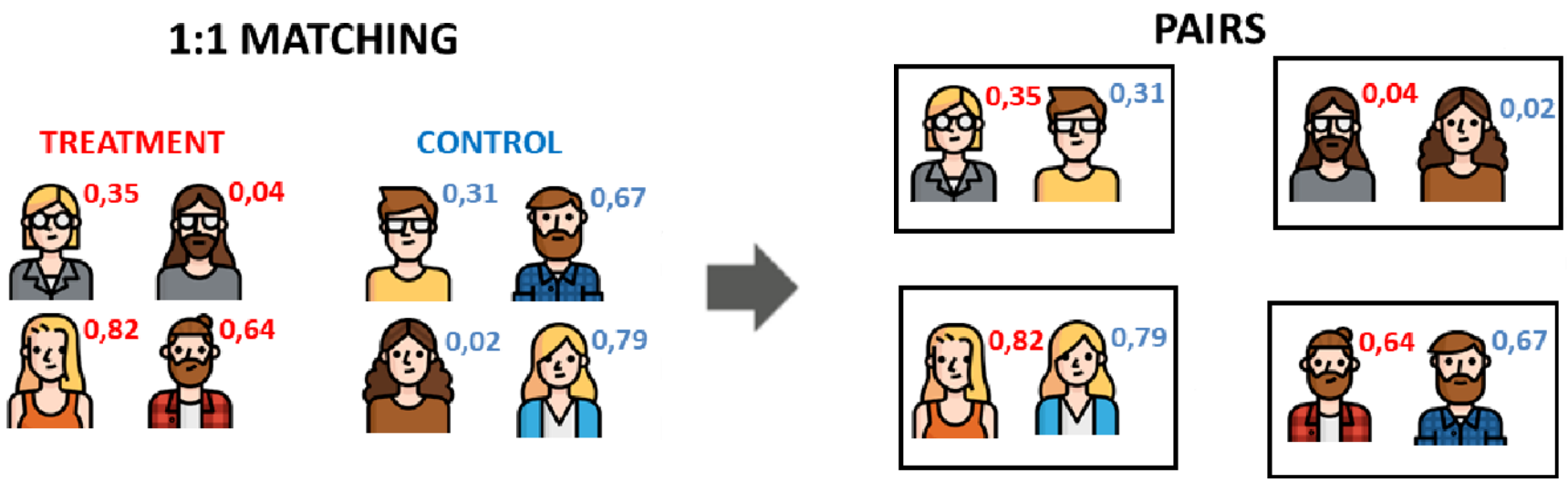
The randomised trial is the preferred study design for evaluating the effectiveness and safety of interventions. Yet such trials can be prohibitively expensive, unethical, or take too long. When it is not possible to carry out a randomised trial, observational data can be used to answer similar questions. Here, we describe the process of using observational data to emulate a target trial, which applies the study design principles of randomised trials to observational studies that aim to estimate the causal effect of an intervention. The target trial provides a formal framework to help avoid self-inflicted biases common to observational studies.

Anthony A Matthews, [1] Goodarz Danaei, [2] Nazrul Islam, [3,4] Tobias Kurth[5]

BMJ 2022; 378

Propensity Score Matching

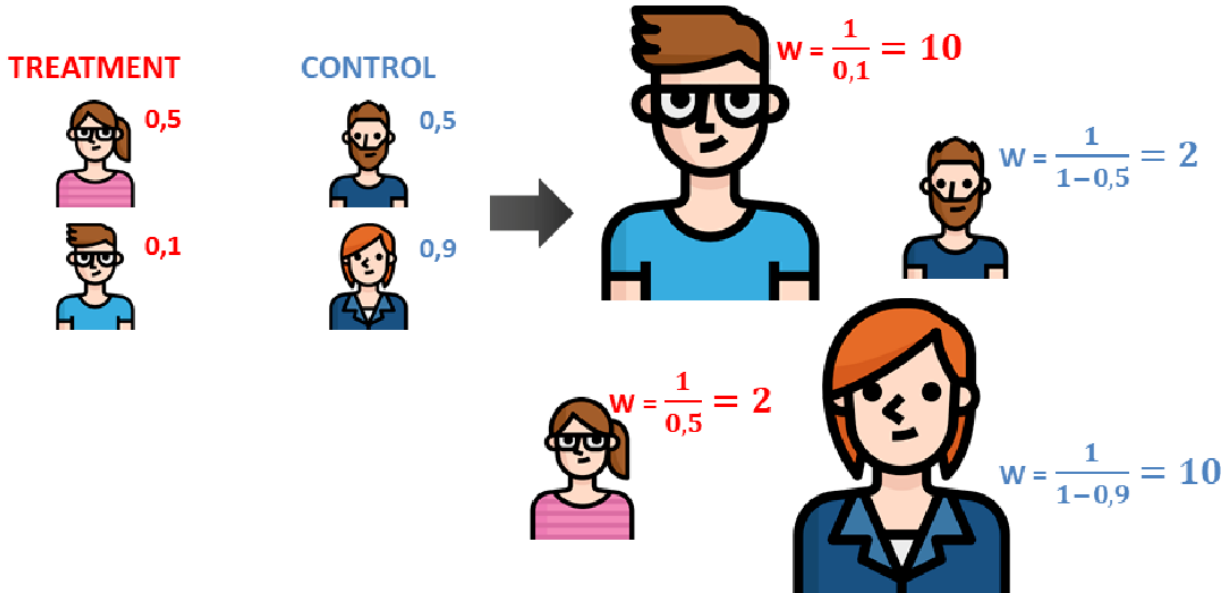
- Propensity Score Matching (PSM) 는 처치군과 같거나 비슷한 Propensity score를 가진 대조군을 매칭하는 방법.



Annaratone, Margherita. "Statistical methods to analyse registry data in a comparative setting." (2018).

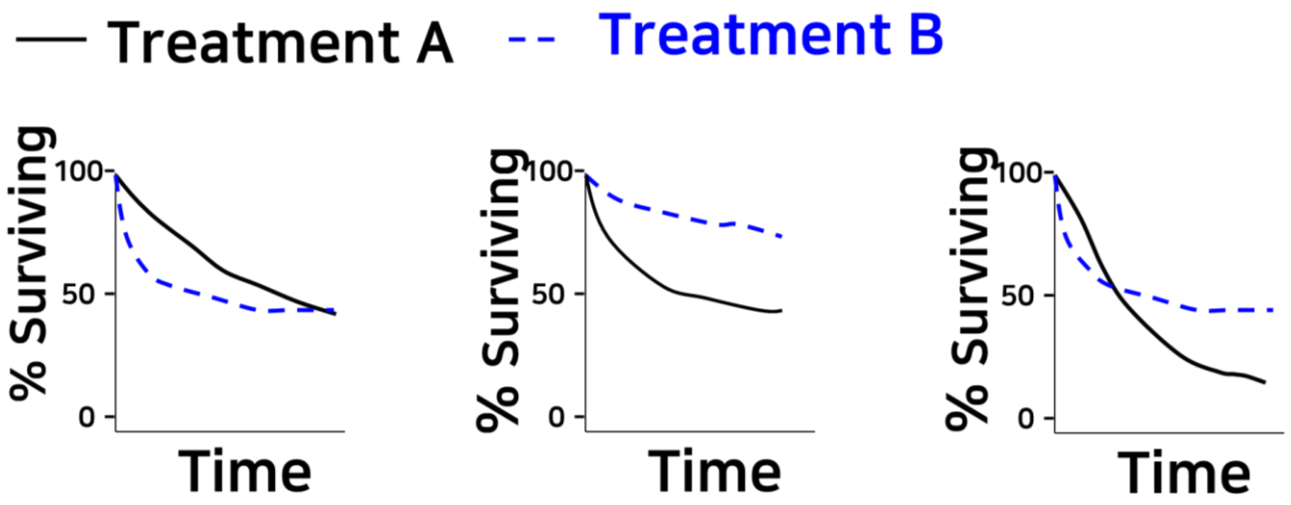
IPTW

- Inverse Probability of Treatment Weighting (IPTW)는 Propensity score로 가중치를 부여하여 혼란변수의 영향을 최소화하는 방법



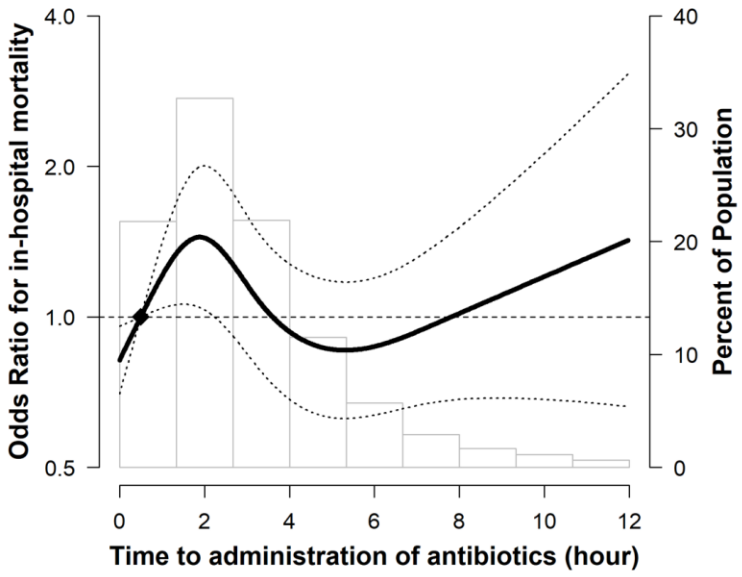
Annaratone, Margherita. "Statistical methods to analyse registry data in a comparative setting." (2018).

Comparing two survival curves



- Time-varying variable
  - The value of the variable (exposure) changes over time
  - The effect of the variable does not change (that is, the HR for a given value of the variable does not change)
- Time-dependent effect (coefficient)
  - The effect of the variable (coefficient / HR) changes over time
  - The value of the variable does not change

선형의 관계가 아닐 수도 있음.



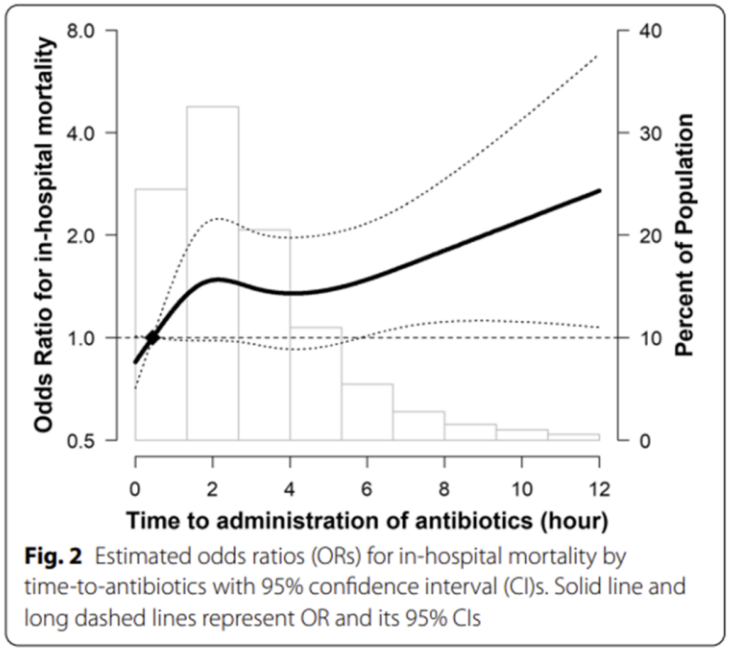


Fig. 2 Estimated odds ratios (ORs) for in-hospital mortality by time-to-antibiotics with 95% confidence interval (CI)s. Solid line and long dashed lines represent OR and its 95% CIs

생물학적 설명가능성 (plausibility)

- Consistency with current biological knowledge about the disease
- But it is based on prior belief or knowledge

기존지식과의 일치 (coherence)

- Interpretation of cause effect relationship dose not conflict with what is known of the natural history and biology of disease
- Absence of coherence cannot be taken as evidence against causality

Table 2. Comparison of 1-year efficacy and safety endpoints according to the use of PPIs.

	Without PPI No. of events	With PPI (1-year cumulative %)	Without (ref) vs with PPI HR (95% CI)
Overall			
Efficacy endpoints			
Major GI bleeding requiring transfusion	236 (0.7)	140 (0.4)	0.59 (0.48-0.73)§
Major or minor GI bleeding with hospitalisation	336 (1.0)	236 (0.7)	0.70 (0.60-0.83)§
Safety endpoints			
MACCE*	4,714 (13.4)	4,619 (13.1)	0.98 (0.94-1.02)
Cardiovascular death	268 (0.8)	295 (0.8)	1.10 (0.93-1.30)
Spontaneous myocardial infarction	2,319 (6.6)	2,345 (6.7)	1.01 (0.96-1.07)
Ischaemic stroke	345 (1.0)	385 (1.1)	1.12 (0.97-1.29)
Repeat revascularisation	2,743 (7.8)	2,600 (7.4)	0.95 (0.90-1.00)
Clopidogrel user			
Efficacy endpoints			
Major GI bleeding requiring transfusion	92 (0.6)	57 (0.4)	0.62 (0.45-0.86)§
Major or minor GI bleeding with hospitalisation	128 (0.8)	102 (0.6)	0.79 (0.61-1.02)
Safety endpoints			
MACCE*	2,332 (14.2)	2,298 (13.8)	0.98 (0.92-1.04)
Cardiovascular death	178 (1.1)	174 (1.1)	0.97 (0.79-1.19)
Spontaneous myocardial infarction	1,093 (6.7)	1,117 (6.7)	1.01 (0.93-1.10)
Ischaemic stroke	195 (1.2)	232 (1.4)	1.18 (0.98-1.43)
Repeat revascularisation	1,330 (8.1)	1,303 (7.9)	0.97 (0.90-1.05)
Prasugrel or ticagrelor user			
Efficacy endpoints			
Major GI bleeding requiring transfusion	145 (0.8)	83 (0.5)	0.58 (0.44-0.76)§
Major or minor GI bleeding with hospitalisation	208 (1.1)	134 (0.7)	0.65 (0.52-0.81)§

실험적 입증 (experiment)

- Strong criterion for causality (if well-designed experiments)

일관성

	Clopidogrel			Prasugrel		
	Treated with a PPI	Not treated with a PPI	Adjusted HR (95% CI)	Treated with a PPI	Not treated with a PPI	Adjusted HR (95% CI)
CV death, MI, or stroke	11·8% (255/2257)	12·2% (526/4538)	0·94 (0·80–1·11)	10·2% (220/2272)	9·7% (423/4541)	1·00 (0·84–1·20)
All-cause death	2·9% (58/2257)	3·3% (139/4538)	0·68 (0·47–0·96)	3·1% (65/2272)	3·0% (123/4541)	1·00 (0·71–1·41)
CV death	2·2% (44/2257)	2·5% (106/4538)	0·71 (0·47–1·07)	2·2% (46/2272)	2·0% (87/4541)	1·06 (0·70–1·62)
MI	9·5% (209/2257)	9·8% (424/4538)	0·98 (0·82–1·17)	7·7% (166/2272)	7·3% (319/4541)	1·02 (0·84–1·25)
Stent thrombosis (ARC definite or probable)	2·4% (50/2150)	2·3% (92/4272)	1·08 (0·75–1·55)	1·1% (22/2159)	1·1% (46/4263)	1·03 (0·60–1·76)
TIMI major or minor bleeding (non-CABG)	4·6% (92/2234)	3·4% (139/4482)	1·13 (0·85–1·49)	4·8% (98/2253)	5·0% (205/4488)	0·92 (0·71–1·18)
TIMI major bleeding (non-CABG)	2·4% (46/2234)	1·6% (65/4482)	1·20 (0·80–1·79)	2·5% (51/2253)	2·4% (95/4488)	0·97 (0·67–1·39)
Net clinical outcome (death, MI, stroke, or TIMI major non-CABG bleeding)	13·9% (299/2257)	13·8% (594/4538)	0·96 (0·83–1·12)	12·6% (268/2272)	12·1% (516/4541)	0·99 (0·85–1·17)

Data are Kaplan-Meier percentage (n/N) unless otherwise stated. Adjusted hazard ratios (HR) (95% CI) indicate the association between PPI use and the risk of clinical outcomes after adjusting for potential confounders and the propensity to treat with a PPI. PPI=proton-pump inhibitor. CV=cardiovascular. MI=myocardial infarction. ARC=Academic Research Consortium. TIMI=Thrombolysis In Myocardial Infarction. CABG=coronary artery bypass graft surgery.

***Table 3*: Kaplan-Meier event rates for efficacy and safety endpoints in the TRITON-TIMI 38 trial**

Lancet 2009; 374: 989–97

연관성의 특이성 (specificity)

- One cause leads to one effect, not multiple effects
- Specificity strengthens evidence for causality, but lack of specificity dose not rule out causality

Additionally, we performed diverse sensitivity analyses for all primary and secondary outcomes to evaluate the robustness of the main findings. First, we redefined the use of exposure as having filled at least 2 benzodiazepine prescriptions during the first trimester. Second, we redefined the outcome definition as the presence of ≥2 diagnoses of congenital malformations. Third, we restricted the study cohort to those who had underlying comorbidities related to the indication for benzodiazepines (bipolar disorder, depression/mood disorder, anxiety, sleep disorder, and gastrointestinal disease) to mitigate confounding by indication. Fourth, we restricted the cohort to nulliparous women to account for intraindividual correlations that might arise from repeated measurements of the same women. Fifth, we conducted a negative control analysis by comparing negative exposure control (defined as pregnancies exposed to benzodiazepines between 180 days and 90 days before the last menstrual period, which is not an etiologically relevant window for congenital malformations) with the reference group in the main analysis (pregnancies not exposed to benzodiazepines in the first trimester). If the main finding is subject to residual confounding, we can expect a non-null result from the negative control analysis. Sixth, for outcomes that presented an increased risk, we used a rule-out approach to explore the impact of unmeasured confounders (e.g., maternal smoking status) (S1 Appendix). Lastly, we conducted a quantitative bias analysis based on the probabilistic method to address the impact of selection bias (S2 Appendix). All analyses were conducted

PLoS Med., 2023 Feb 27;20(2):e1004183 | https://doi.org/10.1371/journal.pmed.1004183

	Benzodiazepine		Unexposed		Relative risk (95% CI)		PS-adjusted relative risk (95% CI)	*p*-value
	No. of Events	No. of Births	No. of Events	No. of Births	Unadjusted	PS-adjusted		
Overall congenital malformations								
Main analysis	2,667	40,846	156,896	3,053,381	1.27 (1.22–1.32)	1.09 (1.05–1.13)		<0.001
Sensitivity analyses								
≥2 prescriptions of exposure	1,690	27,809	156,896	3,053,381	1.18 (1.13–1.24)	1.06 (1.01–1.12)		0.012
≥2 diagnoses of outcome	1,643	40,846	93,602	3,053,381	1.31 (1.25–1.38)	1.10 (1.05–1.16)		<0.001
Restriction to women with main indications	734	11,603	4,303	74,129	1.09 (1.01–1.18)	1.04 (0.96–1.12)		0.375
Restriction to nulliparous women	1,448	20,477	83,422	1,601,759	1.36 (1.29–1.43)	1.12 (1.06–1.18)		<0.001
Negative control analysis	5,951	105,912	149,447	2,922,168	1.10 (1.07–1.13)	1.00 (0.97–1.02)		0.829
Congenital heart defects								
Main analysis	1,588	40,846	83,584	3,053,381	1.42 (1.35–1.49)	1.15 (1.10–1.21)		<0.001
Sensitivity analyses								
≥2 prescriptions of exposure	989	27,809	83,584	3,053,381	1.30 (1.22–1.38)	1.13 (1.06–1.21)		<0.001
≥2 diagnoses of outcome	1,006	40,846	51,156	3,053,381	1.47 (1.38–1.56)	1.19 (1.11–1.27)		<0.001
Restriction to women with main indications	451	11,603	2,378	74,129	1.21 (1.10–1.34)	1.15 (1.03–1.27)		0.012
Restriction to nulliparous women	891	20,477	44,782	1,601,759	1.56 (1.46–1.66)	1.21 (1.13–1.30)		<0.001
Negative control analysis	3,183	105,912	79,605	2,922,168	1.10 (1.07–1.14)	0.99 (0.96–1.03)		0.760

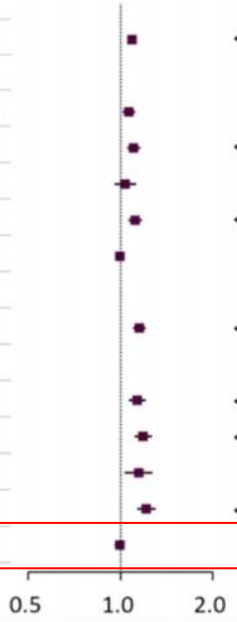


Fig 5. Risks of congenital malformations in infants following maternal exposure to benzodiazepines in the first trimester: sensitivity analyses. CI, confidence interval; PS, propensity score.

PLoS Med., 2023 Feb 27;20(2):e1004183 | https://doi.org/10.1371/journal.pmed.1004183

최신 방법들 !

- Components
  - Aim
  - Eligibility
  - Treatment strategy
  - Treatment assignment
  - Follow-up
  - Outcome
  - Casual contrasts
  - Statistical analysis

Supplement Table 1. Specification and emulation of a target trial evaluating the effect of NOAC versus warfarin on hazards of diabetes complications using real-world data from Taiwan's NHIRD

Component	Target trial	Emulated trial using real-world data
Aim	To estimate the relative effect of NOAC versus warfarin on hazards of diabetes complications and mortality in AF patients with DM	Same
Eligibility	Adult patients aged ≥20 years previously diagnosed with AF and DM without severe valvular heart disease or end stage renal disease No prior use of oral anticoagulants.	Same, but with the exclusion of patients with a previous diagnosis of rheumatic heart disease, congenital heart disease, or who had received valve replacement surgery, because severe valvular heart disease is hard to define using diagnostic codes in NHIRD directly
Treatment strategies	1. Receiving NOAC treatment 2. Receiving warfarin treatment	Same
Treatment assignment	Eligible patients are randomly assigned to either treatment group (the same probability of treatment assignment between the two groups)	Using propensity score approaches to generate a study population with similar probability of treatment assignment between the two groups.
Follow-up	Follow-up begins at treatment assignment and ends at occurrence of diabetes complications, at death, at loss to follow-up, or on 31 December 2018, whichever occurs first	Same (the assignment and initiation of the treatment occur at the same time in the real-world scenario)
Outcome	Macrovascular complications, microvascular complications, glycemic emergency, and mortality	Same
Causal contrast	Primary analysis: ITT effect (i.e., effect of being assigned to NOAC versus warfarin at baseline, regardless of whether patients continue following the assigned treatment after baseline)	Same (using as-started analysis, analog of ITT)
	effect (i.e., effect of following the treatment strategies in the study protocol at baseline and after baseline)	analog of per-protocol)
Statistical analysis	Cox proportional hazards model	Same (except we further applied the shared frailty model accounting for potential cluster-specific random effects from each individual hospital/clinic)

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; NHIRD, National Health Insurance Research Database; NOAC, non-vitamin K antagonist oral anticoagulant; IPTW, inverse probability of treatment weighting; ITT, intention-to-treat