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ORIGINAL RESEARCH

Heterogeneous Effects of Intensive Glycemic and Blood Pressure on Cardiovascular Events Among Diabetes by Living Arrangements

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BACKGROUND: Although living alone versus with others is a key social element for cardiovascular prevention in diabetes, evidence is lacking about whether the benefit of intensive glycemic and blood pressure (BP) control differs by living arrangements. We thus aim to investigate heterogeneity in the joint effect of intensive glycemic and BP control on cardiovascular events by living arrangements among participants with diabetes.

METHODS AND RESULTS: This study included 4731 participants with diabetes in the ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure) trial. They were randomized into 4 study arms, each with glycated hemoglobin target (intensive, <6.0% versus standard, 7.0–7.9%) and systolic BP target (intensive, <120 mm Hg versus standard <140 mm Hg). Cox proportional hazard models were used to estimate the joint effect of intensive glycemic and BP control on the composite cardiovascular outcome according to living arrangements. At a mean follow-up of 4.7 years, the cardiovascular outcome was observed in 445 (9.4%) participants. Among participants living with others, intensive treatment for both glycemia and BP showed decreased risk of cardiovascular events compared with standard treatment (hazard ratio [HR], 0.68 [95% CI, 0.51–0.92]). However, this association was not found among participants living alone (HR, 0.96 [95% CI, 0.58–1.59]). *P* for interaction between intensive glycemic and BP control was 0.53 among participants living with others and 0.009 among those living alone (*P* value for 3-way interaction including living arrangements was 0.049).

CONCLUSIONS: We found benefits of combining intensive glycemic and BP control for cardiovascular outcomes among participants living with others but not among those living alone. Our study highlights the critical role of living arrangements in intensive care among patients with diabetes.

Key Words: cardiovascular events ■ heterogeneity ■ intensive blood pressure control ■ intensive glycemic control ■ living arrangements

Diabetes is a major risk factor for cardiovascular disease (CVD),[1,2] affecting 537 million people worldwide in 2021.[3] In recent years, social determinants of cardiovascular health and diabetes have received substantial attention as they could not only increase the overall risk of disease but also modify the treatment effects.[4–6] Living arrangements could be one such social risk factor related to the prevention of CVD events given that family support is critical to maintaining treatment adherence,[7,8] particularly

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CLINICAL PERSPECTIVE

What Is New?

- In this post hoc analysis of a randomized clinical trial of 4733 individuals, the combination of intensive glycemic control and intensive blood pressure control was associated with decreased risk of cardiovascular disease events among participants living with others.
- However, this association was not found among those living alone, and the 3-way interaction between intensive glycemic control, intensive blood pressure control, and living arrangement was statistically significant.

What Are the Clinical Implications?

- Our findings highlight the importance of considering living arrangements as one of the key social determinants of cardiovascular health that could modify the treatment effect of intensive glycemic and blood pressure control to prevent cardiovascular disease among patients with diabetes.

Nonstandard Abbreviations and Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACCORD-BP	ACCORD-Blood Pressure
SAEs	serious adverse events
SPRINT	Systolic Blood Pressure Intervention Trial

when the treatment includes multiple and intensive approaches.[9–11] Indeed, in a previous secondary analysis of SPRINT (Systolic Blood Pressure Intervention Trial), the intensive blood pressure (BP) control group showed a significantly lower rate of CVD events than standard BP control groups among Black individuals without diabetes living with others but not among those living alone.[12] However, it is not clear whether the benefit of intensively lowering both glucose and BP differs by living arrangements in patients with type 2 diabetes.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was conducted from January 2001 to June 2009 to examine whether intensive treatment to target normal glycated hemoglobin levels (HbA1c<6.0%), as compared with standard treatment (HbA1c 7.0–7.9%), would reduce CVD events among participants with diabetes who had high CVD risk.[13] In the original ACCORD trial, a finding of excess mortality observed in the intensive control group led to early discontinuation after a mean of 3.5 years of follow-up.[13] Following the ACCORD trial, 46.2% of participants were then assigned to an ACCORD-BP (ACCORD-Blood Pressure) trial with a 2-by-2 factorial design, to determine whether intensive treatment to target BP (systolic BP[SBP] <120 mm Hg) would reduce CVD events as compared with standard treatment (SBP <140 mm Hg).[14] Although the investigators did not find a joint effect of intensive glycemic and BP control on CVD outcomes among the entire study sample,[15] no studies have investigated the possible heterogeneity in the treatment effects by participants' living arrangements.

To address this knowledge gap, using ACCORD-BP data, we aimed to examine the heterogeneity in the joint effect of intensive glycemic and BP control on reducing CVD by living arrangements among participants with diabetes. Given the increased demands of intensive therapy, such as heightened adherence and side effect management, our hypothesis posits that the combined effect of these rigorous treatment modalities may vary according to the patient's living situation, which can act as an indicator of social support. As the percentage of US adults living alone is increasing over the past 2 decades,[16] our study would help clinicians and public health professionals better understand such heterogeneity by social risk and potentially advance a tailored approach for CVD management among patients with diabetes.

METHODS

The study protocol is available from Dr Inoue (e-mail, inoue.kosuke.2j@kyoto-u.ac.jp). The statistical code is available from Dr Inoue (e-mail, inoue.kosuke.2j@kyoto-u.ac.jp). The data set is available through National Heart, Lung, and Blood Institute BioLINCC data repository (https://biolincc.nhlbi.nih.gov/).

Data Sources and Study Participants

This is a secondary analysis of the ACCORD-BP trial. The anonymized trial data were obtained through the Biologic Specimen and Data Repository Information Coordinating Center of the National Heart, Lung, and Blood Institute. The detailed design, procedure, recruitment, and outcomes of ACCORD and ACCORD-BP were previously published.[13,14] In brief, both were randomized trials, and the ACCORD-BP trial used a 2-by-2 factorial design to investigate whether more intensive treatment of glycemia or BP or both were effective to decrease the rate of major CVD events, compared with standard treatment. The participants of the ACCORD-BP trial were recruited from January

2001 to October 2005 at 77 clinical sites organized into 7 networks in the United States and Canada. Overall, 10 251 participants with diabetes were assigned to the ACCORD trial and 4733 of them were also assigned to the ACCORD-BP trial.

The eligibility criteria for ACCORD-BP were as follows: (1) type 2 diabetes, (2) a HbA1c level of 7.5% or more, and (3) 40 years of age or older with CVD or 55 years of age or older with atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional risk factors for CVD (dyslipidemia, hypertension, smoking, or obesity). Participants with a body mass index >45, a serum creatinine level >1.5 mg per deciliter, or other serious illnesses were excluded.

The ACCORD-BP trial was reviewed by the Protocol Review Committee appointed by the National Heart, Lung, and Blood Institute. The study protocol was approved by the institutional review board or ethics committee at each center, and informed consent was obtained for all participants. This post hoc study analysis was also approved by the institutional review board at Kyoto University (R3069) and was conducted following the Declaration of Helsinki.

Data Variables

Intervention

All participants were randomly assigned into 4 groups according to treatment arm (target HbA1c <6.0% versus HbA1c 7–7.9%; target SBP <120 mm Hg versus <140 mm Hg). HbA1c was measured every 2 months in intensive glycemic treatment and every 4 months in standard glycemic treatment.[14] During each office visit in ACCORD-BP, BP was measured 3 times while the participant was seated and had been resting quietly for 5 minutes.[14] An automated measurement system (Model 907, Omron Healthcare, Kyoto, Japan) was used for the measurements.

Outcomes

In this study, we adopted the primary outcome of ACCORD-BP, which is the occurrence of major cardiovascular events defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.[17] Trained personnel at each clinical location determined self-reported study results through structured interviews. In addition, medical records and other corroborating data were collected. All study outcomes were assessed using a predetermined procedure without information on treatment allocations. We also calculated the number of serious adverse events (SAEs) that included fatal or life-threatening events resulting in death, persistent disability, or hospitalization or extended hospital stays.[14] These encompassed hypotension, syncope, bradycardia, electrolyte abnormalities, injurious fall, and acute kidney injury or acute renal failure.

Other Covariates

At the time of enrollment in ACCORD-BP, living arrangement (ie, living alone or living with others) was self-reported for the questionnaire "Does the participant live with 1 or more adults?".[14] In this questionnaire, an adult was defined as anyone 18 years of age or older who permanently resides with the participant. Participants also self-reported their age (in years), sex (male or female), race or ethnicity (White, Black, Hispanic, or other), educational attainment (less than high school, high-school graduate, some college, or college degree or higher), and cigarette-smoking status (current, former, or never). Additionally, clinical and laboratory information was collected, including BP, glycated hemoglobin, body mass index, total cholesterol, high-density lipoprotein, estimated glomerular filtration rate, previous cardiovascular events, duration of diabetes, and medication use.[13,14] Any missing data for these baseline variables were filled in using a random forest approach.

Statistical Analysis

After describing baseline characteristics for each treatment arm, we drew a Kaplan–Meier survival curve for the primary outcome (major cardiovascular events) according to each of the four study arms and living arrangements. Then, we employed Cox proportional hazard models with interaction terms between the glycemic treatment arm and BP treatment arm to estimate the hazard ratio (HR) of the primary outcome with 95% CIs for 3 treatment statuses (intensive glycemic and intensive BP group, intensive glycemic and standard BP group, standard glycemic and intensive BP group) compared with standard glycemic and standard BP group according to the living arrangement. As a sensitivity analysis, we adjusted for sex, race and ethnicity, and educational attainment to account for the potential imbalance of these social determinants of health between the participants living with others and those living alone.

Additionally, we examined the trends in mean HbA1c levels and mean SBP levels across each group by living arrangement. Lastly, we compared the occurrence of SAEs according to treatment arm and living arrangement given the possible increased risk of SAEs due to intensive glycemic and BP control. All analyses were performed by R (version 4.2.1) from September 2022 to May 2023.

RESULT

The flow of study sample selection is shown in Figure 1. Of 4731 participants included in this study, the

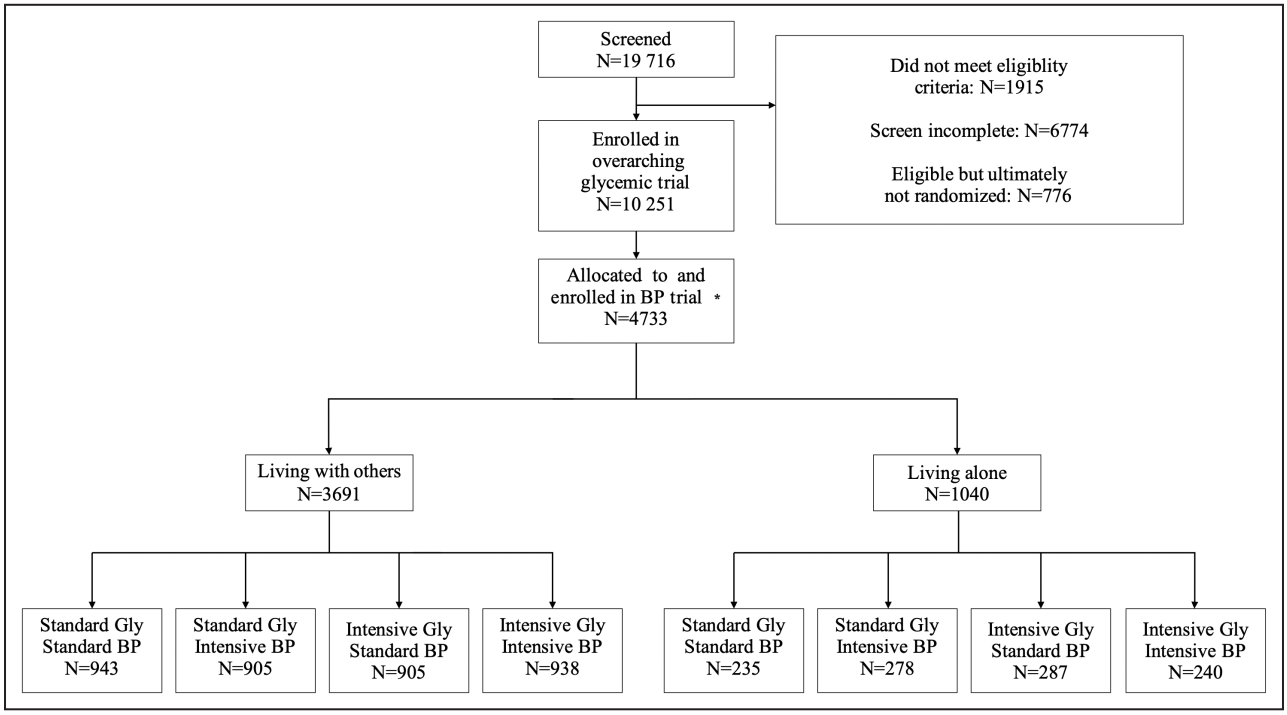

Figure 1. Flow of the study sample selection.
*Missing covariates were imputed by random forest algorithm. Two participants who were missing living arrangement status were excluded. In the ACCORD trial, living with others was defined as participants permanently living with 1 or more adults over 18 years old. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes-Blood Pressure; BP, blood pressure; and Gly, glycemic.

mean±SD age was 62.7 (6.7) years and 2256 (47.7%) were female. Among study participants, 1040 were living alone and 3691 were living with others (2 participants who were missing living arrangement status were excluded.). Participants living alone were more likely to be female, Black, and have obesity compared to those living with others (Table). Covariate distribution was well balanced across the 4 treatment groups among both participants living with others (Table S1) and those living alone (Table S2).

Joint Effect of Intensive Glycemic and BP Control on CVD Event Reduction by Living Arrangement

Mean±SD follow-up time was 4.7 (1.5) years and the primary composite cardiovascular outcome was observed in 445 (9.4%) adults: 339 (9.2%) of 3691 participants living with others, and 106 (10%) of 1040 participants living alone. We found no evidence of the difference in the incidence of primary outcome by living arrangement status (HR, 1.12 [95% CI, 0.89–1.38]).

During the follow-up, participants in the intensive glycemic and intensive BP group were more likely to have 3 or more oral medications (living with others: 71.3%, living alone: 65.4%) than in the standard glycemic and standard BP group (living with others: 45.4%, living alone: 40.4%). Detailed numbers of each component of the primary outcome (ie, death from CVD, nonfatal myocardial infarction, nonfatal stroke) are shown in Table S3.

Among participants living with others, intensive treatment for both glycemia and BP showed the largest reduction in cardiovascular events compared with standard treatment for both (HR, 0.68 [95% CI, 0.51–0.92]), followed by the other 2 groups (standard glycemic and intensive BP group, HR, 0.77 [95%, CI 0.57–1.03]; and intensive glycemic and standard BP group; HR, 0.77 [95% CI, 0.58–1.03]) (Figure 2A). When we included the multiplicative interaction term between intensive glycemic control and intensive BP control, HR for the interaction term was 1.15 and *P* for interaction was 0.53.

Among participants living alone, intensive treatment for both glycemia and BP did not show a decreased risk of CVD events compared with standard treatment for both (HR, 0.96 [95% CI, 0.57–1.59]), whereas the intensive glycemic and standard BP group showed the largest reduction of CVD risk (HR, 0.48 [95% CI, 0.27–0.84]) followed by the standard glycemic and intensive BP group (HR, 0.73 [95% CI, 0.43–1.22]) (Figure 2B). When we included the multiplicative interaction term between intensive glycemic control and intensive BP

Table. Baseline Characteristics of the Study Participants by Living Arrangement Status

Variables	Living with others N=3691	Living alone* N=1040
Female sex, %	43.9%	61.2%
Age, y, mean±SD	62.5±6.6	63.6±6.7
Race and ethnicity, %		
White	60.1%	54.1%
Black	20.6%	35.1%
Hispanic	7.5%	5.0%
Others†	11.8%	5.8%
Educational attainment, %		
Less than high school	16.3%	16.7%
High school	27.0%	26.4%
Some college	32.4%	32.2%
College degree or higher	24.4%	24.7%
Current smoking, %	12.8%	14.6%
Body mass index, mean±SD, kg/m²‡	32.0±5.4	32.6±5.7
Obesity, %	60.5%	64.9%
Blood pressure, mean±SD, mm Hg		
SBP	139.2±15.5	139.3±17.1
DBP	75.9±10.2	76.1±11.0
Glycated hemoglobin, mean±SD, %	8.3±1.1	8.4 ±1.1
Total cholesterol, mean±SD, mg/dL	191.6±44.4	196.6±45.6
Low density lipoprotein, mean±SD, mg/dL	109.1±36.3	113.0±38.0
High density lipoprotein, mean±SD, mg/dL	45.7±13.2	48.4±15.1
Estimated glomerular filtration rate, mean±SD, mL/min/1.73 m²	92.3±29.1	89.3±27.1
Duration of diabetes, y	10.9±7.7	11.2±8.1
≥10 y, %	50.3%	49.4%
Hypertension (SBP≥140, DBP≥90), %	47.4%	47.4%
History of cardiovascular disease, %§	34.1%	32.0%

DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

*In the ACCORD (Action to Control Cardiovascular Risk in Diabetes-Blood Pressure) trial, living with others was defined as participants permanently living with 1 or more adults over 18 years old.

†Others was defined as the the self-report of one or more of the following: American Indian/Alaska Native, First Nation (Aboriginal Canadian), Asian, Native Hawaiian/Other, Pacific Islander, French Canadian, Other.

‡Body mass index was calculated as weight in kilogram divided by the square of height in meters. Obesity was defined as body mass index ≥30 kg/m².

§Cardiovascular disease was defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

control, HR for the interaction term was 2.79 and *P* for interaction was 0.010. The *P* value for the 3-way interaction (intensive glycemic control, intensive BP control, and living arrangement) was 0.049.

We found the consistent results when we adjusted for sex, race and ethnicity, and educational attainment in our Cox proportional hazard models (Table S4).

Trends in HbA1c and SBP According to Treatment Assignment and Living Arrangement

When we assessed the trends in HbA1c, the standard glycemic control group (either intensive or standard BP) showed similar trends regardless of living arrangement (Figure 3A and 3B). Despite wide CIs due to small sample size in each subgroup, HbA1c levels in the intensive glycemic and intensive BP group tended to show higher HbA1c levels compared with the intensive glycemic and standard BP group among people in the living alone group. In addition, we observed higher HbA1c levels in the living alone group compared to living with others group at some points (Table S5). When we assessed the trends in SBP, we found consistent trends over time among both standard and intensive SBP control groups regardless of living arrangement (Figure 3C and 3D).

Hypoglycemia and Serious Adverse Events

Hypoglycemia occurred in 489 (13.2%) participants living with others, and 139 (13.4%) participants living alone (Table S6). SAEs occurred in 92 (2.5%) participants living with others, and 33 (3.3%) participants living alone (*P* value, 0.27). The prevalence of hypoglycemia and SAEs was higher among the intensive glycemic and intensive BP control arms than other treatment arms.

DISCUSSION

In this post hoc analysis of ACCORD-BP, the combination of intensive glycemic control and intensive BP control was associated with decreased risk of CVD events among participants living with others, whereas this association was not found among those living alone. We found a significant interaction between intensive glycemic control, intensive BP control, and living arrangement. These findings highlight the importance of considering living arrangements as one of the key social determinants of cardiovascular health that could modify the treatment effect of intensive glycemic and BP control to prevent CVD for patients with diabetes.

To the best of our knowledge, this is the first study to take living arrangements into account when assessing the joint effect of intensive glycemic and BP control on CVD event prevention. Ample evidence has well documented the role of living alone as a significant risk factor for incident CVD.[9–11] In addition, a previous secondary analysis of SPRINT found the heterogeneity in the treatment effect of intensive BP control on CVD prevention by living arrangement among Black individuals without diabetes.[12] However, there remains a gap in research concerning intensive glycemic control

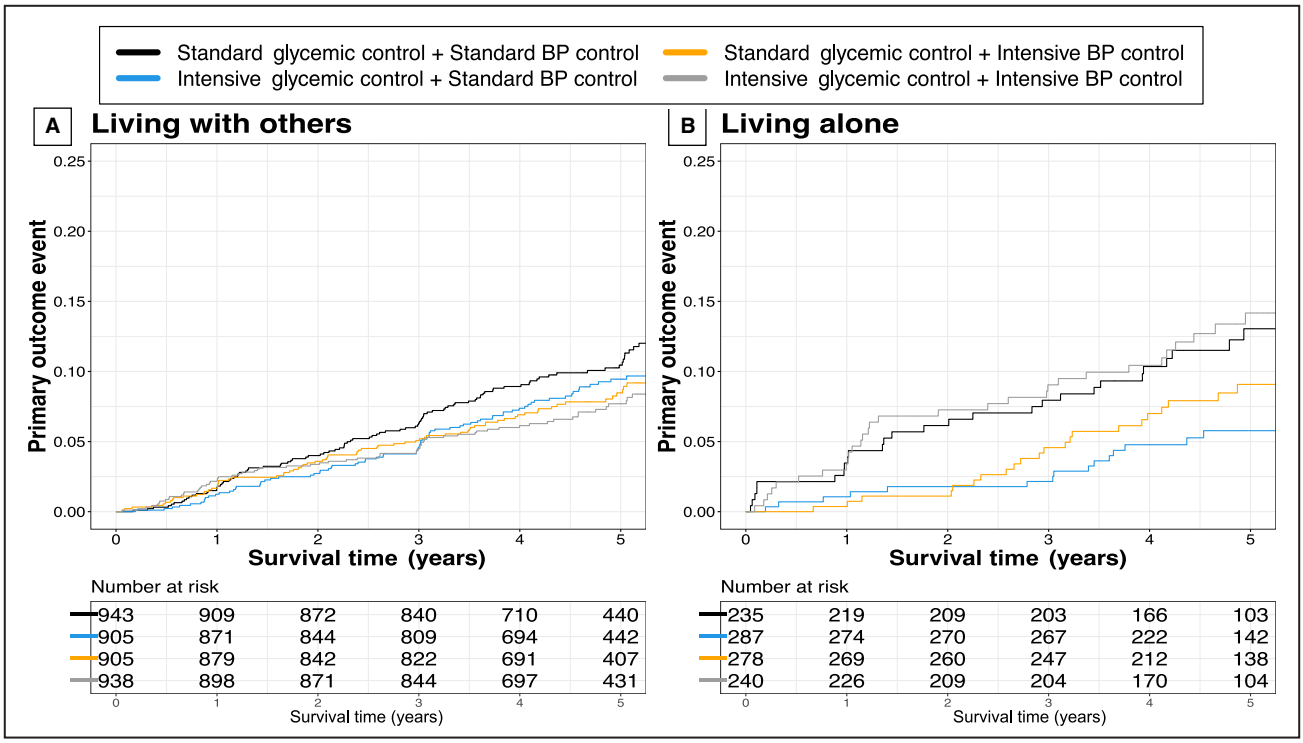

Figure 2. Kaplan–Meier survival curve for cardiovascular events according to glycemic treatment (intensive vs standard glycemic control) and blood pressure treatment (intensive vs standard blood pressure control) among patients living alone vs those living with others.

In the ACCORD trial, living with others was defined as participants permanently living with 1 or more adults over 18 years old. **A**, Among patients living with others, HR for the interaction term between intensive glycemic control and intensive BP control was 1.15 and *P*-for interaction was 0.53. **B**, Among patients living alone, HR for the interaction term was 2.79 and *P* for interaction was 0.010. The *P* value for the 3-way interaction (intensive glycemic control, intensive BP control, and living arrangement) was 0.049. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes-Blood Pressure; BP, blood pressure; and HR, hazard ratio.

among individuals with diabetes. This lack of evidence is particularly concerning given the rising prevalence of adults living alone and diabetes in the United States.[16,18] It is essential to address this knowledge gap toward the American Heart Association's 2030 Impact Goal,[19] which seeks to enhance healthy life expectancy equitably for all. In this context, our study makes a valuable contribution by elucidating the differential effects based on social determinants like living arrangements, thereby providing a more nuanced understanding of personalized treatment approaches of jointly managing glycemic and BP levels intensively.

Although the underlying mechanism is unclear, we considered the following 3 possible explanations of our findings. First, adherence to behavioral change interventions under the large demand of intensive care (ie, intensive control for both glucose levels and BP) may vary based on living arrangements. Prior research has demonstrated that individuals living alone are less likely to engage in physical activities than those living with others.[20] This challenge, possibly stemming from a lack of social support, could become more pronounced with the introduction of intensive care for both glycemic and BP control. Cognitive overload by these joint interventions (ie, multitasking) may also lead to lower adherence to a healthy lifestyle in some participants. Indeed, in our data, mean HbA1c levels in the intensive glycemic and BP control group were generally higher in individuals living alone compared to those living with others, indicating potentially inadequate glycemic control for people living alone. Moreover, such behavioral change interventions can reduce the risk of cardiovascular events via pathways other than glycemic and BP controls (eg, weight reduction and improvement of cholesterol levels). Because poor adherence to medications and behavioral change interventions are associated with worse outcomes among patients with type 2 diabetes,[21–24] further research is needed to assess our hypothesis and elucidate the differential impacts of intensive control on adherence based on living situations.

Second, those living alone may face challenges in medication adherence, a consequence of social isolation and complex treatment regimens in the intensive care for both glycemic and BP control. This hypothesis is supported by data from our study, showing a

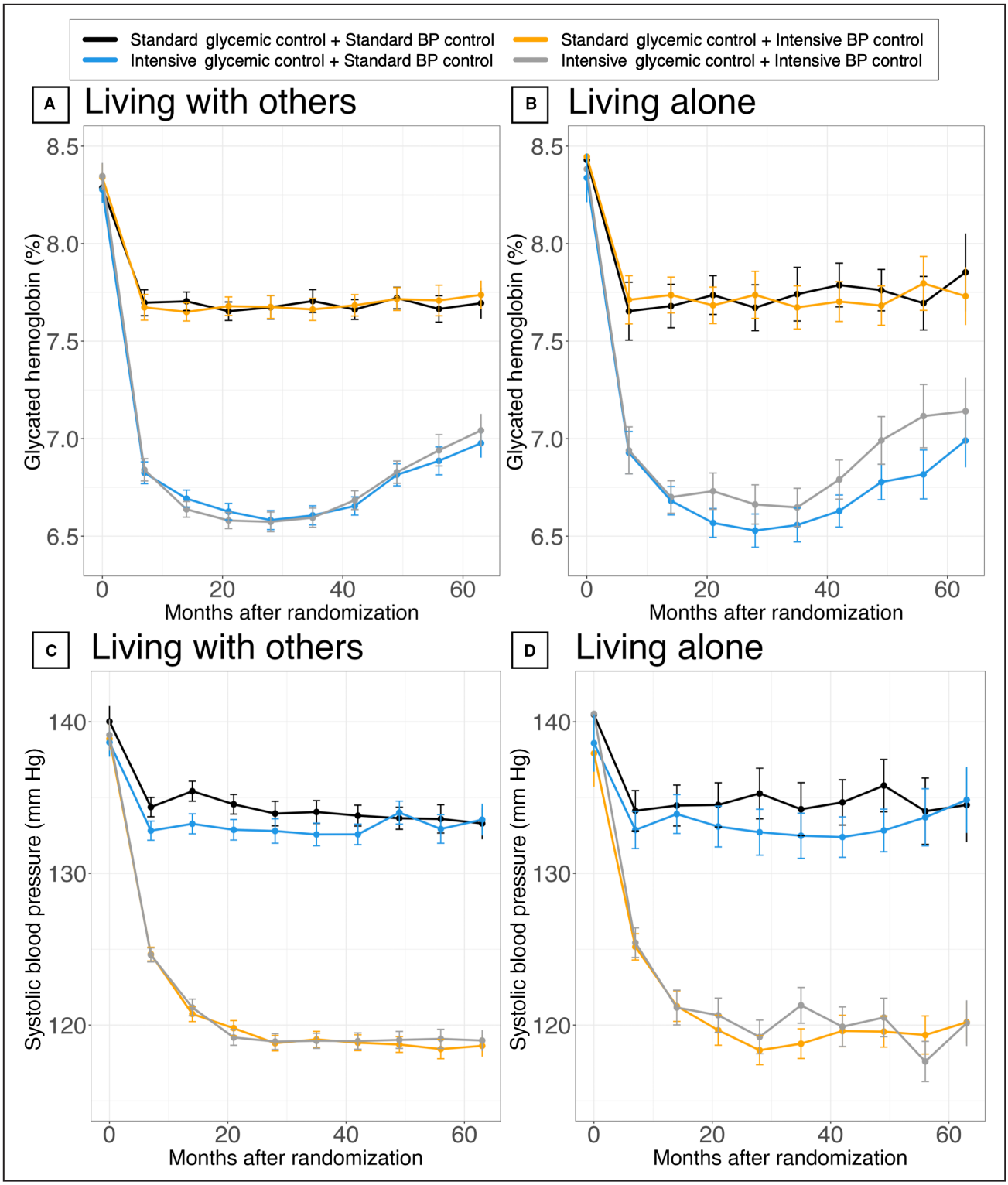

Figure 3. Mean HbA1c and systolic blood pressure levels at each study visit according to treatment assignments among patients living alone vs those living with others.
In the ACCORD trial, living with others was defined as participants permanently living with one or more adults over 18 years old. (**A**) mean HbA1c levels among people living with others. (**B**) mean HbA1c levels among people living alone. (**C**) mean systolic blood pressure among people living with others. (**D**) mean systolic blood pressure among people living alone. ACCORD indicates Action to Control Cardiovascular Risk in Diabetes-Blood Pressure; BP, blood pressure; and HbA1c, glycated hemoglobin.

higher reliance on multiple medications in intensive treatments; the prevalence of people taking 3 or more oral medications was higher in the intensive glycemic and intensive BP (living with others: 71.3%, living alone: 65.4%) compared with the standard glycemic and standard BP group (living with others: 45.4%, living alone: 40.4%).

Lastly, although we found no difference in the frequency of SAEs or other adverse events, the availability of subsequent care and immediate medical support could be influenced by living arrangements. For example, the rate of survival following out-of-hospital cardiac arrest is significantly associated with a concomitant increase in bystander cardiopulmonary resuscitation.[25] Thus, living alone or with others could be critical in emergency scenarios such as out-of-hospital cardiac arrests, where rapid intervention (eg, bystander cardiopulmonary resuscitation) can be lifesaving.[25] All 3 mechanisms should also be explored in future studies.

There are several limitations to our study. First, the participants were randomly assigned by BP and glycemic treatments but not by living arrangements, and thus randomization was not guaranteed across each treatment arm in our study. However, we checked that the measured covariates were well balanced across the arms. Second, the recent pharmacologic approach for diabetes is different from that of the ACCORD trial. In addition to antidiabetic agents used in the ACCORD,[26] the current guidelines in diabetes care include the recommendations of sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and dipeptidyl peptidase 4 inhibitors.[27] Given that incorporating sodium–glucose cotransporter 2 inhibitors or glucagon-like peptide 1 receptor agonists in the treatment regimen has a benefit for CVDs,[27] our results may not be generalizable to the current approach in diabetes care. Third, as living arrangements are strongly affected by countries and their culture, our findings may not also be transportable to other countries with different cultures. Fourth, we collected the information on living arrangements (whether participants lived with 1 or more adults or not) only at baseline and thus could not consider whether the participants changed their living arrangement status during the trial. Furthermore, we did not have information on with whom they were living. Because we defined living with others based on a questionnaire about living with 1 or more adults over 18 years old, some people such as widows or widowers living with children were included in a living alone group. We also lacked data on other elements associated with social isolation, including marital status and social involvement. Therefore, our findings may not directly reflect the impact of social isolation, which requires further research with detailed information on interaction with families and friends.

CONCLUSIONS

In conclusion, we found a joint effect of intensive glycemic and intensive BP treatment on cardiovascular prevention among individuals with diabetes living with others but did not find this effect among those living alone. This finding suggests that living arrangement status and specifically living alone, one of the key components of social isolation, may modify the beneficial effect of intensive medical care for diabetes and hypertension to prevent CVD, which should be validated in future prospective studies.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6

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