Association of Smartphone-Recorded Steps Over Years and Change in Cardiovascular Risk Factors Among Working-Age Adults

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BACKGROUND: Few data exist on long-term steps and their relation to changes in cardiovascular disease risk factors. We aimed to examine the associations using long-term smartphone-recorded steps.

METHODS AND RESULTS: The present analysis made use of data from 2 national databases and a commercial app database. We evaluated the associations between smartphone-recorded daily steps over 2 years and 2-year changes in the cardiovascular disease risk factors. A total of 15,708 participants with mean (SD) age of 44.1 (9.5) and 23.5% women were included. After adjustment for potential confounders, differences in weight were almost linearly associated with 2-year steps in men (estimate [SE] per 1000 steps/d: −0.33 [0.029] kg), and inversely related only above 5000 steps/d in women (−0.18 [0.054] kg). An inverse linear association with systolic blood pressure was observed in men (−0.34 [0.097] mm Hg) but not in women. Greater steps were associated with change in high-density lipoprotein cholesterol and triglycerides (0.61 [0.068] and −3.4 [0.61] mg/dL in men; 0.64 [0.17] and −2.3 [0.67] mg/dL in women), while changes in low-density lipoprotein cholesterol were evident in men only (−0.59 [0.17] mg/dL). A significant negative association with hemoglobin A1c was observed only in women (−0.012 [0.0043] %).

CONCLUSIONS: In a large cohort of Japanese adults, smartphone-recorded steps over years were associated with beneficial changes in cardiovascular disease risk factors, with some differences between men and women in the associational patterns. The findings support the benefit of long-term physical activity for cardiovascular disease health and suggest a useful role of smartphone-recorded steps for monitoring cardiovascular disease risk over the long term.

Key Words: cardiovascular disease ■ glucose metabolism ■ mobile health ■ physical activity ■ smartphone ■ step counts ■ weight loss

Accumulated evidence has shown many health benefits of physical activity. Ambulation, including intentional walking (eg, for exercise or transportation), can be measured with step counters; thus, daily step counts can be a surrogate marker for total volume of physical activity. A goal of daily steps, commonly set at 10,000, has been investigated in recent studies, and a recent systematic review demonstrated that each additional 1000 steps/d taken, even <10,000 steps, is associated with decreased risk of mortality, cardiovascular disease mortality, and morbidity. However, most of the studies assessed daily steps only over a short period (eg, 7 days), which may not represent participants' true steps over the long term. Furthermore, evaluation of changes in average daily steps can help lend support for a causal relation of step counts with health outcomes in observational studies, which has not been well investigated, except for a recent study on cardiorespiratory fitness.

Smartphones currently are able to capture step counts continuously and thus can collect data on
long-term daily steps. Indeed, a recent expert panel highlighted evidence regarding steps and health outcomes as a major evidence gap requiring more investigation. To fill these knowledge gaps, in this study, we pragmatically used smartphone-recorded consecutive daily steps over a period of years to examine their association with change in CVD-related biomarkers in a large cohort of working-age adults. We hypothesized that the associations are nonlinear and may differ for different risk factors.

Methods
Data described in this article will not be publicly available because of the confidentiality agreement related to the data. Analytic code will be made available upon request pending application and approval. The requirement for obtaining written informed consent from the participants was waived. The study protocol was approved by the Institutional Review Board of the Harvard T.H. Chan School of Public Health (Boston, Massachusetts). Further information is available in Data S1.

Study Population
The present analysis made use of data from the Japanese national health check-up database, the Japanese government health insurance claims database, and a commercial app database (kencom, developed by DeSC Healthcare Inc.). Business companies in Japan are responsible for the health of employees and their families, offering free annual health check-ups that are taken by almost all of those qualified. The annual health check-up results, including biomarkers of CVD risk, are stored in the health check-up database. Information from the health insurance claims database was leveraged to ascertain the use of medications for hypertension, hypercholesterolemia, and diabetes. "kencom" is a free app on both iOS and Android platforms that can be used by the workers and their families who belong to the society-managed, employment-based health insurance association (public sector) affiliated with DeSC Healthcare Inc. The app was designed to promote the users' physical activity through various means including friendly competition. The kencom database records daily step information of the app users. More detailed information on the present database is available in Data S1.

The present analysis targeted working-age adults living in Japan. To be included in the present study, participants had to undergo an annual health check-up between April 2015 and November 2020 ("baseline health check-up") and a second health check-up 24 to 35 months after the baseline health check-up ("follow-up health check-up"), hereafter referred to as "2-year" data. The participants had to download and register on kencom between April 2015 and November 2020, and have step data available in the kencom database from 1 year before the registration date (the app can pull in step data before the registration date) and all the way through to the follow-up health check-up. Step data were defined as being available if information was present on at least 20 days each month, for 12 consecutive months before, and through all months until the follow-up health check-ups. We excluded those for whom step data might be inaccurate, which we defined as having high variance in baseline steps as well as steps during the period between the baseline and follow-up health check-ups (top 5 percentile variance of monthly averaged steps for each). From N=17,222 participants with baseline information, N=15,662 participants were included in the main analysis. In secondary analyses, we assessed steps over 1 year (instead of 2 years) as the exposure and 1-year changes in CVD biomarkers as the outcome.

Assessment of Steps
The primary exposure of interest was the smartphone-recorded average daily step count between the 2 annual health check-up assessments (as noted above, 24 to 35 months apart and referred to as “2-year steps”). We averaged step counts over the consecutive 24 to 35 months between the baseline and follow-up health
check-ups. Additionally, to control for the starting level of activity, we also defined “baseline steps” as mean daily steps over 12 consecutive months before the baseline health check-up, which was used as a covariate in analyses. This study design is summarized in Figure 1.

CVD Risk Assessment
The primary outcomes were 2-year changes (ie, baseline to follow-up health check-ups, in the following CVD-related biomarkers: weight (kg), BMI (kg/m²), waist (cm), systolic BP (sBP; mm Hg), diastolic BP (dBP; mm Hg), HDL cholesterol (HDL-c; mg/dL), LDL cholesterol (LDL-c; mg/dL), triglyceride (mg/dL), fasting plasma glucose (FPG; mg/dL), and hemoglobin A1c (HbA1c) (%). sBP and dBP were averaged over 2 measurements taken at each health examination. Data on these biomarkers were obtained from the national health check-up database.

Covariate Assessment
Age, sex, smoking status, and alcohol consumption were assessed during the annual health check-ups, which were ascertained from the health check-up database. The use of lipid-lowering drugs, glucose-lowering drugs, and antihypertensive drugs was defined as use within 3 months before the baseline health check-ups, and the information was ascertained from the health insurance claims database.

Figure 1. Study design.
The exposure consecutively measured averaged step counts over 2 years, and the outcomes were 2-year changes in CVD risk factors including weight, body mass index, waist, systolic and diastolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting plasma glucose, and HbA1c. Laboratory data were ascertained in the baseline and follow-up (24–35 months after baseline) health check-ups. Models were adjusted for baseline demographics and laboratory data as well as baseline steps measured over 1 year before the participant’s baseline health check-up. CVD indicates cardiovascular disease; and HbA1c, hemoglobin A1c.

Statistical Analysis
Continuous data were expressed as mean±SD or median (interquartile range). Missing values were generally few as summarized in Table S1 and complete cases were used for every analysis.

We a priori determined to conduct sex-stratified analyses using separate models because of potentially huge differences in phone wear between sexes.8 We estimated the associations between the 2-year steps and changes in CVD risk factors using multivariate generalized additive models with use of cubic spline function of steps. The models were adjusted for age (continuous), BMI (continuous), current smoking (yes/no), current alcohol drinking (yes/no), use of lipid-lowering drugs (yes/no), glucose-lowering drugs (yes/no), and antihypertensive drugs (yes/no) at baseline health check-up, baseline steps (continuous), and the months between baseline and follow-up health check-ups (continuous). We also adjusted the models for the related baseline CVD risk with respect to each outcome; that is, baseline waist (cm) for waist difference, baseline sBP (mm Hg) for sBP difference, and baseline dBP (mm Hg) for dBP difference, baseline HDL-c (mg/dL) for HDL-c difference, baseline LDL-c (mg/dL) for LDL-c difference, baseline triglyceride (mg/dL) for triglyceride difference, baseline FPG (mg/dL) for FPG difference, and baseline HbA1c (%) for HbA1c difference outcomes. We visualized the nonlinear associations using the R package “ggeffects” by setting the covariates reference values.11 We also used linear regressions to estimate the slopes of change in risk factors in relation to average daily steps. We further analyzed the associations between steps and changes in CVD risks stratified by high/low baseline steps, defined as above/below the median value separately for each sex.

In the post hoc analyses, we evaluated the effect measure modifications by sex, testing the interactions between steps and sex in the generalized additive models based on the models using whole population for each outcome.

As secondary analyses, we assessed the associations between 1-year steps and 1-year changes in the CVD risks. The definitions of the exposure and outcomes were parallel to main analyses with step counts averaged over the consecutive 12 to 23 months (hereafter referred to as “1-year steps”) between baseline and 1-year follow-up health check-ups (also separated by 12 to 23 months), and changes in CVD-related biomarkers from baseline to 1-year follow-up health check-ups.

We used false discovery rate (FDR) for the statistical inferences given 10 outcomes of interest in each sex (20 comparisons). Multiple testing for the interactions was also adjusted by FDR (10 outcomes). All analyses were performed using R 3.6.1 (The R Foundation).
RESULTS

Table 1 summarizes the characteristics of the study participants. A total N=11,986 men and N=3,722 women were included in the main analysis. The mean (SD) age was 44.1 (9.5) years, and median (interquartile range) BMI was 22.8 (20.8, 24.9) kg/m². Men were more likely to drink alcohol, be a current smoker, and have worse CVD risk profiles compared with women, although the median values of every CVD-related biomarker were within normal range in either sex. Characteristics of the population included versus excluded in the main analysis are summarized in Table S2.

Figure S1 depicts the histograms of smartphone-recorded 2-year steps of the main populations stratified by sex. Smartphone-recorded steps were higher in men than in women; the median (interquartile range) 2-year steps were 6,674 (5,202, 8,147) steps/d in men and 5,027 (3,650, 6,491) steps/d in women. Baseline steps and 2-year steps were strongly correlated with Spearman correlation coefficient of 0.88.

Figures 2–5 illustrate the associations of 2-year steps and changes in CVD risks in covariate-adjusted generalized additive models stratified by sex. The statistics are summarized in Table 2. In general, higher steps were associated with favorable changes in CVD risk; however, there were some differences in the associational patterns according to sex for several CVD risk factors. Null associations were observed for selected biomarkers. Stratified analysis by the baseline steps are illustrated in Figure S2.

Weight and Waist

Two-year steps were almost linearly and inversely associated with the changes in weight or BMI in men over the observed range of steps (Figure 2). In women, an inverse relation was clear only above 5,000 steps/d. The associations for changes in weight or BMI in men; the median (interquartile range) 2-year steps were 6,674 (5,202, 8,147) steps/d in men and 5,027 (3,650, 6,491) steps/d in women. Baseline steps and 2-year steps were strongly correlated with Spearman correlation coefficient of 0.88.

Blood Pressure

Two-year steps were inversely associated with changes in SBP and DBP in men, while no statistically significant association was observed in women (FDR=0.004 for continuous variables). BMI indicates body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; IQR, interquartile range; and LDL, low-density lipoprotein.

with low baseline steps, decreases in weight and waist were observed only above 5,000 steps/d; while in those with high baseline steps, there were inverse linear associations similar to those in men, with x-intercepts of 9,000 to 10,000 steps (Figure S2B).

Table 1. Baseline Characteristics

|                     | Men        | Women       |
|---------------------|------------|-------------|
| At baseline health check-up |            |             |
| Age, y              | 44.4 (9.7) | 43.1 (9.6)  |
| Alcohol drinking    | 7961 (78.4)| 1701 (54.6) |
| Current smoking     | 2590 (21.6)| 195 (5.2)   |
| BMI, %              | 23 [21, 25]| 21 [19, 23] |
| Waist, cm           | 82 [78, 88]| 75 [70, 82] |
| Systolic BP, mmHg   | 120 [111, 129]| 110 [101, 120] |
| Diastolic BP, mmHg  | 75 [68, 83] | 68 [61, 76] |
| HDL cholesterol, mg/dL | 57 [49, 67]  | 70 [61, 81] |
| LDL cholesterol, mg/dL | 122 [103, 142]| 112 [94, 133] |
| Triglyceride, mg/dL | 94 [67, 139]| 64 [48, 88] |
| Fasting plasma glucose, mg/dL | 93 [87, 100]| 88 [83, 94] |
| HbA1c, %            | 5.4 [5.2, 5.6]| 5.4 [5.2, 5.6] |
| Use of antihypertensive drug | 1185 (9.9)  | 169 (4.5)  |
| Use of glucose-lowering drugs | 302 (2.5)  | 31 (0.8)   |
| Use of lipid-lowering drugs | 965 (8.1)  | 161 (4.3)  |
| At follow-up health check-up |            |             |
| BMI, %              | 23.4 [21.6, 25.5]| 21.1 [19.5, 23.6] |
| Waist, cm           | 82 [78, 89]  | 76 [71, 83] |
| Systolic BP, mmHg   | 121 [112, 130]| 111 [102, 122] |
| Diastolic BP, mmHg  | 77 [69, 84]  | 69 [62, 77] |
| HDL cholesterol, mg/dL | 57 [49, 67]  | 71 [61, 82] |
| LDL cholesterol, mg/dL | 124 [105, 144]| 117 [98, 139] |
| Triglyceride, mg/dL | 95 [67, 141] | 67 [49, 92] |
| Fasting plasma glucose, mg/dL | 94 [88, 101]| 89 [84, 95] |
| HbA1c, %            | 5.4 [5.2, 5.6]| 5.4 [5.2, 5.6] |
| Steps               |            |             |
| Interval of health check-ups, mo | 30 [26, 36]  | 30 [26, 36] |
| Baseline steps, steps/d | 6656 [5161, 8218]| 5003 [3498, 6503] |
| 2-year steps, steps/d | 6674 [5202, 8147]| 5027 [3650, 6491] |

Values are n (%) for categorical variables and mean (SD) or median (IQR) for continuous variables.
and 0.001 in men and FDR=0.98 and 0.28 in women, respectively, for sBP and dBP; Figure 3). The inverse associations in men were almost linear in sBP and linear in dBP. Each additional 1000 steps/d over 2 years was associated with −0.33 (0.096) mm Hg and −0.27 (0.070) mm Hg changes in sBP and dBP, respectively. FDRs for the interaction between steps and sexes were 0.026 for sBP and 0.021 for dBP. Reduction in blood pressure over 2 years was observed in those with >10 000 to 15 000 steps/d in each sex.

In men with lower baseline steps, the reductions in sBP and dBP with higher steps were not statistically significant, while there were significant inverse linear relationships in men with higher baseline steps (Figure S2C). The associations in women were not significant in either stratum of baseline steps (Figure S2D).

**Lipids**

There were robust positive relationships between steps and HDL-c in either sex (FDR <0.001; Figure 4). HDL-c was higher by 0.60 (0.068) and 0.69 (0.16) mg/dL for each additional 1000 steps/d, averaged over 2 years, in men and women, respectively. LDL-c was linearly and inversely associated in men (−0.54 [0.18] mg/dL per 1000 steps/d, FDR=0.004), while there was no statistically significant association in women (FDR=0.31). The associations for triglyceride were linearly inverse in both sexes, with −3.3 (0.60) and −2.2 (0.66) mg/dL changes per 1000 steps/d in men and women, respectively. The associational patterns were statistically different according to sexes (FDR-interactions <0.001 for HDL-c, =0.007 for LDL-c, and =0.004 for triglyceride). The favorable changes in HDL-c or triglyceride were observed above 5000 to 7500 step/d, while not clearly detected in LDL-c in the observed range of steps. In men, the associations for the slopes were similar in magnitude between low and high baseline step groups in HDL-c and triglyceride; however, in contrast to the low baseline step groups, no significant associations were observed in LDL-c in men with high baseline steps (Figure S2E). Overall, relationships in women were similar in stratified and nonstratified analyses except for the

**Table 2. Association of 2-Year Steps and Changes in CVD Risks**

| Variable            | Sex     | N   | EDF | FDR   | β     | SE   | FDR   | FDR-interaction |
|---------------------|---------|-----|-----|-------|-------|------|-------|----------------|
| **Weight, kg**      | Men     | 10 175 | 1.89 | <0.001 | −0.32 | 0.029 | <0.001 | <0.001         |
|                     | Women   | 3105 | 3.38 | 0.003  | −0.17 | 0.052 | 0.003  |                |
| **BMI, kg/m²**      | Men     | 10 173 | 1.77 | <0.001 | −0.11 | 0.010 | <0.001 | 0.003         |
|                     | Women   | 3105 | 3.26 | 0.003  | −0.070 | 0.021 | 0.003  |                |
| **Waist, cm**       | Men     | 9859 | 7.02 | <0.001 | −0.37 | 0.032 | <0.001 | <0.001         |
|                     | Women   | 2961 | 3.23 | 0.004  | −0.25 | 0.075 | 0.004  |                |
| **Systolic BP, mmHg** | Men   | 10 173 | 1.41 | 0.004  | −0.33 | 0.096 | 0.004  | 0.026         |
|                     | Women   | 3105 | 1.00 | 0.98   | −0.004 | 0.20  | 0.98   |                |
| **Diastolic BP, mmHg** | Men   | 10 172 | 1.00 | 0.001  | −0.27 | 0.070 | <0.001 | 0.021         |
|                     | Women   | 3105 | 1.00 | 0.28   | −0.17 | 0.14  | 0.28   |                |
| **HDL-c, mg/dL**    | Men     | 10 070 | 3.92 | <0.001 | 0.60  | 0.068 | <0.001 | <0.001         |
|                     | Women   | 10 067 | 1.00 | <0.001 | 0.69  | 0.16  | <0.001 |                |
| **LDL-c, mg/dL**    | Men     | 10 070 | 1.00 | 0.004  | −0.54 | 0.18  | 0.004  | 0.009         |
|                     | Women   | 3083 | 1.00 | 0.31   | 0.39  | 0.37  | 0.31   |                |
| **Triglyceride, mg/dL** | Men   | 10 070 | 1.00 | <0.001 | −3.3  | 0.60  | <0.001 | 0.007         |
|                     | Women   | 3083 | 1.00 | 0.002  | −2.2  | 0.66  | 0.002  |                |
| **FPG, mg/dL**      | Men     | 8609 | 1.00 | 0.023  | −0.22 | 0.093 | 0.023  | 0.077         |
|                     | Women   | 2684 | 1.00 | 0.025  | −0.33 | 0.14  | 0.025  |                |
| **HbA1c, %**        | Men     | 9887 | 1.00 | 0.31   | −0.0028 | 0.0027 | 0.31   | 0.52          |
|                     | Women   | 3008 | 1.00 | 0.004  | −0.013 | 0.0043 | 0.004  |                |

Models were fitted separately for each sex. These were adjusted for age (continuous), BMI (continuous), current smoking (yes/no), alcohol drinking (yes/no), use of lipid-lowering drugs (yes/no), glucose-lowering drugs (yes/no), and antihypertensive drugs (yes/no) at baseline health check-up, baseline steps (continuous), months between the baseline and follow-up health check-ups, and related baseline CVD risk with respect to each outcome (eg, baseline waist [continuous] for waist difference).

In GAMs, cubic spline function was applied to steps. Interactions between steps and sex were tested in the GAMs based on the whole population. Multiple testing was accounted with use of FDR for 20 comparisons in the sex-stratified analyses and 10 comparisons for interaction tests.

BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; EDF, effective degrees of freedom; FDR, false discovery rate; FPG, fasting plasma glucose; GAM, generalized additive model; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; low-density lipoprotein cholesterol; and LDL-c, low-density lipoprotein cholesterol.
association with triglyceride in those with high baseline steps, which were not linear (Figure S2F).

**Glucose Metabolism**

Two-year steps was significantly, inversely associated with changes in FPG in either sex (FDR=0.023 in men and 0.025 in women) and changes in HbA1c only in women (−0.013 [0.0043] % changes per 1000 step/d, FDR=0.004; Figure 5). However, there was no significant interaction between HbA1c and sex (FDR-interaction=0.52). The favorable changes were observed above ≈7500 steps/d in both sexes.

In the stratified analysis, no significant associations were observed in men (Figure S2G). In women, the inverse relationships with either FPG
or HbA1c were stronger in those with high baseline steps compared with those with low baseline steps (Figure S2H).

**Secondary Analysis Using Steps Over 1 Year**

N=26,884 participants were included in the secondary analyses of the associations between 1-year steps and 1-year (ie, 12 to 23 months) changes in CVD-related biomarkers. There were no major differences in characteristics of participants included in the 2- and 1-year step analysis (Table S3).

The results of these secondary analyses are summarized in Figure S3 and Table 3. In general, the associations with changes in CVD risks were weaker and less robust using 1-year instead of 2-year steps.

One-year steps were inversely associated with change in weight only in men (FDR<0.0001 in men and FDR=0.44 in women), and the slope in men was less steep compared with 2-year steps (−0.24 [0.019] kg per 1000 steps/d; Figure S3A). One-year steps were also significantly associated with waist changes only in men (−0.27 [0.022] cm per 1000 steps/d; FDR<0.001), not in women (FDR=0.37).

The associations of 1-year steps with BP were significant only in men, and the associations were weaker than for 2-year steps (−0.26 [0.071] mm Hg and −0.21 [0.052] mm Hg per 1000 steps/d for sBP and dBP, respectively; Figure S3B).

In contrast to 2-year steps, 1-year steps were not significantly associated with changes in LDL-c in both sexes or with triglyceride in women (Figure S3C). The associations for HDL-c were similar with 1-year steps (0.60 [0.049] mg/dL and 0.74 [0.12] mg/dL per 1000 steps/d in men and women, respectively).

Finally, 1-year steps were not associated with changes in FPG in both sexes, and were associated with changes in HbA1c only in women (Figure S3D).
DISCUSSION

In a large cohort of working-age adults living in Japan, smartphone-recorded step counts over 24 to 35 months were associated with favorable changes or slowed worsening in various CVD risk factors, after accounting for baseline steps and other covariates. The associational patterns differed according to the specific risk factors and sex. Differences in weight or waist were almost linearly associated in inverse fashion with steps among men, but only >5000 steps/d in women. The inverse associations with blood pressure were observed in men but not women. Inverse changes in HDL-c and triglyceride with higher steps were noted in both sexes, whereas the association with LDL-c was observed only in men. For glucose biomarkers, only

**Figure 4.** Associations of 2-year step volume and changes in lipid-related biomarkers. Figures show sex-specific, nonlinear associations of 2-year steps as steps/d (x-axis) and 2-year changes of HDL-c (mg/dL), LDL-c (mg/dL), and triglyceride (mg/dL) (each: y-axis). These associations were assessed by generalized additive models with cubic spline functions of 2-year steps, adjusted for age, BMI, current smoking, alcohol drinking, use of lipid-lowering drugs, glucose-lowering drugs and antihypertensives at baseline health check-up, baseline steps, and months between baseline and follow-up health check-ups; and additionally for the related lipid biomarker with respect to each outcome. Gray shadows show the 95% CIs. BMI indicates body mass index; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; and TG, triglyceride.
HbA1c was inversely related to steps among women, while the interaction was not significant. The results for 1-year steps were generally weaker compared with those from 2-year steps. Together with data from other studies, the present results suggest that using smartphone-recorded daily steps might be one clinically useful tool for assessing CVD health.

The present study not only helps address a gap in knowledge by using mass step data measured with wearables, but also provides an important contribution in the association of daily steps with CVD risk factors by investigating change in the risk factors. Previous large-scale cohort studies examining step counts generally averaged over a week have also shown inverse associations with incident CVD. The present study suggests that these associations were likely mediated in part by beneficial changes in weight, waist, BMI, HDL-c, and triglyceride. A recent systematic review reported mixed findings on the association of step counts with dysglycemia, although large cohort studies have consistently shown beneficial associations of higher steps with glucose metabolism. We observed significant inverse associations of 2-year steps with change in HbA1c in women, which may indicate the need for longer-term activity.

Data on the contribution of physical activity on CVD risks have been inconclusive or less evident in randomized controlled trials and mendelian randomization studies. Importantly, the Generation 100 randomized trial showed little effects of 5-year prescribed exercise training on CVD risks in older adults in Norway. However, the implication from the trial was limited because of the very active population at baseline (i.e., even the control group was very active) and low compliance to intervention arms over the 5 years. Mendelian randomization studies demonstrate inconclusive effects of physical activity on CVD, and these results may reflect genetic variants being weak instruments for physical activity, potentially leading to null associations. While our present results are in line with many cohort associations.

Figure 5. Associations of 2-year step volume and changes in glucose-related biomarkers.
Figures show sex-specific, nonlinear associations of 2-year steps as steps/d (x-axis) and 2-year changes of fasting glucose (FPG, mg/dL) and HbA1c (%) (each: y-axis). These associations were assessed by generalized additive models with cubic spline functions of 2-year steps, adjusted for age, BMI, current smoking, alcohol drinking, use of lipid-lowering drugs, glucose-lowering drugs, and antihypertensives at baseline health check-up, baseline steps, and months between baseline and follow-up health check-ups; and additionally for the related baseline glucose biomarker with respect to each outcome. Gray shadows show the 95% CIs. BMI indicates body mass index; FPG, fasting plasma glucose; and HbA1c, hemoglobin A1c.
studies suggestive of physical activity being associated with a better CVD risk profile, additional rigorous studies are needed to infer causality.

One strength of the present study based on smartphone-recorded steps is that it is highly pragmatic and translatable for public health recommendations. Overall, within the observed range of steps, most CVD risks showed favorable associations (or less worsening) with higher step counts. In particular, 2-year steps of ≈7500 steps/d, congruent with previous studies noting a plateauing of mortality risk reduction at this level,4,5 corresponded to the level for favorable/unfavorable changes (ie, x-intercepts) in weight and waist in both sexes. Favorable changes were observed around this cutoff for HLD-c, triglyceride, and glucose metabolism, whereas greater step counts would be needed for blood pressure or LDL-c. One limitation of note is that smartphone-recorded steps may underestimate true step counts since the phone is not always carried. A previous study of iPhone-recorded steps observed an undercount of steps measured by an accelerometer worn all the time, by 12%.8 Differences were larger among those who noted they did not always carry their phone, and also among women (who may be less likely to always carry their phone).8 It is possible that the present nonsignificant associations among women with lower baseline steps may be partly because of less accurate measurement of steps because of noncarrying of phones, since some significant associations were observed in women with higher baseline steps.

Another limitation was that many qualified participants did not undergo the follow-up health check-ups because of unspecified reasons, including job change into nonaffiliated companies, switching national insurance type, opting not to undergo the check-up, and death or serious comorbidities at the period of follow-up health check-up. Such selection might induce bias; however, the associational patterns in 1-year and 2-year steps were similar, and the latter associations were more pronounced, consistent with the dose–response where higher cumulative steps should have greater health impact, suggestive of capturing overall less biased signals. Analyses adjusting for medications

| Table 3. Association of 1-Year Steps and Changes in CVD Risks |
|-----------------|-----------------|-------------|-------------|--------|--------|
|                      | GAM          | Linear regression |
|                      | EDF            | FDR           | β            | SE   | FDR   |
| Weight, kg          | Men N=17 139 | 3.92 <0.001 | −0.24 | 0.019 | <0.001 |
|                      | Women N=5396 | 2.16 0.44 | −0.007 | 0.035 | 0.83  |
| BMI, kg/m²          | Men N=17 136 | 3.13 <0.001 | −0.082 | 0.006 | <0.001 |
|                      | Women N=5395 | 2.07 0.44 | −0.006 | 0.014 | 0.68  |
| Waist, cm           | Men N=16544 | 4.69 <0.001 | −0.27 | 0.022 | <0.001 |
|                      | Women N=5154 | 1.00 0.37 | −0.060 | 0.053 | 0.37  |
| Systolic BP, mmHg   | Men N=17 137 | 1.97 0.003 | −0.26 | 0.071 | <0.001 |
|                      | Women N=5399 | 3.09 0.37 | −0.11 | 0.15  | 0.64  |
| Diastolic BP, mmHg  | Men N=17 135 | 1.00 <0.001 | −0.21 | 0.052 | <0.001 |
|                      | Women N=5399 | 1.00 0.63 | −0.006 | 0.11  | 0.67  |
| HDL-c, mg/dL        | Men N=16981 | 4.10 <0.001 | 0.60 | 0.049 | <0.001 |
|                      | Women N=5356 | 1.61 <0.001 | 0.74 | 0.12  | <0.001 |
| LDL-c, mg/dL        | Men N=16979 | 4.61 0.12 | −0.31 | 0.13  | 0.038 |
|                      | Women N=5355 | 1.11 0.68 | 0.14 | 0.27  | 0.67  |
| Triglyceride, mg/dL | Men N=16980 | 4.67 <0.001 | −2.5 | 0.46  | <0.001 |
|                      | Women N=5356 | 1.00 0.28 | −0.70 | 0.53  | 0.28  |
| FPG, mg/dL          | Men N=14 748 | 5.03 0.28 | −0.098 | 0.070 | 0.27  |
|                      | Women N=4707 | 1.96 0.44 | −0.065 | 0.12  | 0.67  |
| HbA1c, %            | Men N=16814 | 1.00 0.12 | −0.0036 | 0.0019 | 0.12  |
|                      | Women N=5232 | 1.00 0.14 | −0.0067 | 0.0032 | 0.14  |

Models were fitted separately for each sex. These were adjusted for age (continuous), BMI (continuous), current smoking (yes/no), alcohol drinking (yes/no), use of lipid-lowering drugs (yes/no), glucose-lowering drugs (yes/no), and antihypertensive drugs (yes/no) at baseline health check-up, baseline steps (continuous), months between the baseline and follow-up health check-ups, and related baseline CVD risk with respect to each outcome (eg, baseline waist (continuous) for waist difference).

In GAMs, cubic spline function was applied to steps.

Multiple testing was accounted with use of FDR for 20 comparisons in the sex-stratified analyses.

BMI indicates body mass index; BP, blood pressure; CVD, cardiovascular disease; EDF, effective degrees of freedom; FDR, false discovery rate; FPG, fasting plasma glucose; GAM, generalized additive model; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; and LDL-c, low-density lipoprotein cholesterol.
prescribed during the follow-up period provided findings similar to the main analyses, supporting the reliability. While it is possible that the development of incident serious diseases could have caused a person to miss the follow-up health examination, this is less likely because the pool of participants was in general healthy adults who were working for companies or their families. Additionally, individuals with major comorbidities or previous serious diseases are likely covered by other national health insurance in Japan and were not included in this study. Reverse causation is also possible; worsening health and CVD biomarkers led to a decrease in steps, rather than that more steps led to better CVD biomarkers. Different study designs are needed to address the limitation. Although physical activity and CVD risk factors are in part genetically influenced, we did not have any genetic information on participants. Finally, the study population was drawn from healthy individuals living in Japan who had registered on the kenco app and may be limited generalizability in the findings.

CONCLUSIONS

In a large cohort of working-age adults living in Japan, smartphone-recorded steps over 24 to 35 months were associated with beneficial changes in various CVD risk factors after accounting for potential confounders. In particular, robust linear associations were found for changes in weight, waist, BMI, HDL-c, and triglyceride in both sexes. Distinct patterns of association were observed in selected factors between sexes. As such, smartphone-recorded daily steps may be a clinically useful tool to help gauge CVD health.

ARTICLE INFORMATION

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R.H. received consultancy fees from DeSC Healthcare, Inc. M.M. is an employee of DeSC Healthcare Inc. K.M. is a representative director (medical doctor) of DeSC Healthcare Inc. I.L. has no disclosures to report.

Supplemental Material
Data S1. Data structure.
Tables S1-S3.
Figures S1-S3.

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Supplemental Material
Data S1.

Data structure

The data of the present study was based on completely anonymized data from the following three databases:
• Step data from the kencom database
• Prescription data from Japanese health insurance claims database
• Biomarker data from Japanese health check-up databases

Data is aggregated, anonymized and stored in the affiliated local SHIs (society-managed, employment-based health insurance associations), which are public sector entities (similar to the local government) responsible for the employees and the families of the SHI-affiliated companies and which manage the three databases.
Annual health check-ups are offered to the employees and the families of the SHI-affiliated companies for free, and the data is stored in the SHI’s health check-up database.

SHI offers universal, national health insurance for the employees and the families of SHI-affiliated companies. This insurance covers anybody belonging to the SHI-affiliated companies. The insurance covers any medical/dental procedure, for which records are stored in the receipt database.

kencom is a healthcare app developed by DeSC Healthcare, Inc., a private technology company. DeSC Healthcare, Inc. has contrasts with each SHI for the usage of the app. Each SHI pays the subscription fee to DeSC Healthcare, Inc., and the employees and the families of the SHI-affiliated companies can use the app for free. This makes sense because each SHI wants to reduce healthcare costs by improving their employees and their families’ health. Smartphone-recorded daily steps are stored in the kencom database held by DeSC Healthcare. Inc. However, the kencom database itself has little information regarding the overall health without integrating the other two databases. By law, a private company cannot use non-anonymized health check-up data and insurance data for any purpose. Therefore, DeSC Healthcare, Inc. gives the kencom data to each SHI, and asks each SHI to anonymize all three databases and integrate them. Then, DeSC Healthcare Inc. gathers fully anonymized, integrated data from different SHIs, making a large, longitudinal dataset (Figure).

The data anonymization is conducted under the “opt-out agreement” between the users and the SHIs, in which the users are notified of the usage of their data and they can request the deletion of their data. The study complies with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices.

**Data content**
Japanese health check-up database consists of the questionnaires, physical exams, measurement of biomarkers, and imaging exams conducted annually for the majority of adults living in Japan. The Japanese health insurance claims database records monthly information about the patient demographics, diagnoses according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), medical procedures, and medications. The kencom database is mainly about daily physical activity data and the app usage.
Table S1. Counts of missing values

|                                | Missing counts |
|--------------------------------|----------------|
| **Baseline Health Check-up**   |                |
| Age                            | 0              |
| Sex                            | 0              |
| Smoking                        | 0              |
| Alcohol drinking               | 0              |
| BMI                            | 47             |
| Waist                          | 712            |
| Systolic BP                    | 38             |
| Diastolic BP                   | 38             |
| HDL cholesterol                | 177            |
| LDL cholesterol                | 180            |
| Triglyceride                   | 177            |
| Fasting plasma glucose         | 1735           |
| HbA1c                          | 1261           |
| Use of antihypertensives       | 0              |
| Use of glucose lowering drugs  | 0              |
| Use of lipid lowering drugs    | 0              |
| **Follow-up Health Check-up**  |                |
| BMI                            | 12             |
| Waist                          | 338            |
| Systolic BP                    | 10             |
| Diastolic BP                   | 11             |
| HDL cholesterol                | 53             |
| LDL cholesterol                | 55             |
| Triglyceride                   | 53             |
| Fasting plasma glucose         | 1018           |
| HbA1c                          | 561            |

BP, blood pressure
### Table S2. Baseline characteristics according to the inclusion/exclusion of the main analysis

|                                | Excluded from the main analysis | Included in the main analysis |
|--------------------------------|---------------------------------|-------------------------------|
|                                | N=13,958                         | N=15,708                      |
| **At Baseline Health Check-up**|                                 |                               |
| Age, years                     | 44.2 (10.5)                      | 43.9 (9.5)                    |
| Men                            | 10685 (76.6)                     | 11986 (76.3)                  |
| Alcohol drinking               | 8248 (70.6)                      | 9690 (72.8)                   |
| Current smoking                | 2542 (18.2)                      | 2791 (17.8)                   |
| BMI, %                         | 22.8 [20.8, 25.0]                | 22.7 [20.8, 24.9]             |
| Waist, cm                      | 81 [75, 88]                      | 81 [75, 87]                   |
| Systolic BP, mmHg              | 119 [109, 128]                   | 118 [108, 128]                |
| Diastolic BP, mmHg             | 74 [66, 82]                      | 73 [66, 81]                   |
| HDL cholesterol, mg/dL         | 60 [51, 71]                      | 60 [50, 71]                   |
| LDL cholesterol, mg/dL         | 120 [101, 141]                   | 119 [100, 141]                |
| Triglyceride, mg/dL            | 85 [60, 128]                     | 85 [60, 126]                  |
| Fasting plasma glucose, mg/dL  | 92 [86, 99]                      | 92 [86, 99]                   |
| HbA1c, %                       | 5.4 [5.2, 5.6]                   | 5.4 [5.2, 5.6]                |
| Use of antihypertensive        | 1487 (10.7)                      | 1328 (8.5)                    |
| Use of glucose lowering drugs  | 354 (2.5)                       | 328 (2.1)                     |
| Use of lipid lowering drugs    | 1113 (8.0)                       | 1098 (7.0)                    |

Values are n (%) for categorical variables and mean (SD) or median (IQR) for continuous variables.

The table is a comparison between included population in the 2-year analysis vs. those not included because of no availability of 2-year follow-up labs (but 1-year follow-up labs were available) or insufficient step data.

BP, blood pressure
Table S3. Baseline characteristics by analysis

|                             | Two-year analysis | One-year analysis |
|-----------------------------|-------------------|------------------|
|                             | N=15,708          | N=26,884         |
| **At Baseline Health Check-up** |                   |                  |
| Age, years                  | 44.1 (9.5)        | 44.1 (9.9)       |
| Men                         | 11986 (76.3)      | 20370 (75.8)     |
| Alcohol drinking            | 9692 (72.8)       | 16237 (71.9)     |
| Current smoking             | 2785 (17.7)       | 4843 (18.0)      |
| BMI, %                      | 22.8 [20.8, 24.9] | 22.8 [20.8, 25.0]|
| Waist, cm                   | 81 [75, 87]       | 81 [75, 87]      |
| Systolic BP, mmHg           | 118 [108, 128]    | 118 [108, 128]   |
| Diastolic BP, mmHg          | 73 [66, 81]       | 74 [66, 82]      |
| HDL cholesterol, mg/dL      | 60 [51, 71]       | 60 [51, 71]      |
| LDL cholesterol, mg/dL      | 119 [100, 141]    | 120 [100, 141]   |
| Triglyceride, mg/dL         | 85 [60, 127]      | 86 [60, 127]     |
| Fasting plasma glucose, mg/dL| 92 [86, 99]   | 92 [86, 99]      |
| HbA1c, %                    | 5.4 [5.2, 5.6]    | 5.4 [5.2, 5.6]   |
| Use of antihypertensive     | 1354 (8.6)        | 2587 (9.6)       |
| Use of glucose lowering drugs| 333 (2.1)        | 619 (2.3)        |
| Use of lipid lowering drugs | 1126 (7.2)        | 2034 (7.6)       |
| **At Follow-up Health Check-up** |                   |                  |
| BMI, %                      | 23.0 [21.0, 25.2] | 22.9 [20.9, 25.1]|
| Waist, cm                   | 82 [76, 88]       | 82 [76, 88]      |
| Systolic BP, mmHg           | 119 [109, 129]    | 119 [109, 129]   |
| Diastolic BP, mmHg          | 75 [67, 83]       | 75 [67, 82]      |
| HDL cholesterol, mg/dL      | 60 [51, 71]       | 60 [51, 71]      |
| LDL cholesterol, mg/dL      | 123 [103, 143]    | 122 [102, 142]   |
| Triglyceride, mg/dL         | 86 [61, 129]      | 87 [61, 130]     |
| Fasting plasma glucose, mg/dL| 92 [87, 100]   | 92 [87, 100]     |
| HbA1c, %                    | 5.4 [5.2, 5.6]    | 5.4 [5.2, 5.6]   |
| **Steps**                   |                   |                  |
| Interval of health check-ups, months | 30 [26, 36] | 20 [14, 24]    |
| Baseline steps, steps/day   | 6283 [4711, 7885] | 6224 [4649, 7805]|
| Steps (exposure), steps/day | 6295 [4781, 7817] | 6192 [4677, 7769]|

Values are n (%) for categorical variables and mean (SD) or median (IQR) for continuous variables.
BP, blood pressure
Figure S1: Histograms of 2-year steps by sex

A. 2-year step volume in men

B. 2-year step volume in women
Figure S2: Associations of two-year steps and changes in CVD-related biomarkers stratified by baseline steps

A. Men
   - Low baseline steps
   - High baseline steps

   Weight
   - Graphs showing weight difference against step volume

   BMI
   - Graphs showing BMI difference against step volume

   Waist
   - Graphs showing waist difference against step volume

B. Women
   - Low baseline steps
   - High baseline steps

   Weight
   - Graphs showing weight difference against step volume

   BMI
   - Graphs showing BMI difference against step volume

   Waist
   - Graphs showing waist difference against step volume
Figures show sex-specific, non-linear associations of two-year step volume as steps/day (x-axis) and two-year changes of weight (kg), BMI (kg/m²), and waist (cm) (A); systolic and diastolic blood pressure (BP, mmHg) (B); HDL-cholesterol
(HDL-c, mg/dL), LDL-cholesterol (LDL-c, mg/dL) and triglyceride (TG, mg/dL) (C); and fasting glucose (FPG, mg/dL) and HbA1c (%) (D) (each: y-axis), stratified by sex-specific medians of the baseline steps (men: 6,656 steps/day; women: 5,003 steps/day). These associations were assessed by generalized additive models with cubic spline functions of two-year step volume, adjusted for age, BMI, current smoking, alcohol drinking, use of lipid lowering drugs, glucose lowering drugs and antihypertensives at baseline health check-up, baseline steps, and months between baseline and follow-up health checkups. The models were also adjusted for the related baseline CVD risk with respect to each outcome (e.g. baseline waist in the model of waist changes). Grey shadows show the 95% confidence intervals.
Figure S3: Associations of one-year steps and changes in CVD-related biomarkers

A. Men
Weight

BMI

Waist

B. Men
sBP

dBP

Women

Women
Figures show sex-specific, non-linear associations of one-year step volume as steps/day (x-axis) and one-year changes of weight (kg), BMI (kg/m²), and waist (cm) (A); systolic and diastolic blood pressure (BP, mmHg) (B); HDL-cholesterol
(HDL-c, mg/dL), LDL-cholesterol (LDL-c, mg/dL) and triglyceride (TG, mg/dL) (C); and fasting glucose (FPG, mg/dL) and HbA1c (%) (D) (each: y-axis). These associations were assessed by generalized additive models with cubic spline functions of one-year step volume, adjusted for age, BMI, current smoking, alcohol drinking, use of lipid lowering drugs, glucose lowering drugs and antihypertensives at baseline health check-up, baseline steps, and months between baseline and follow-up health checkups. The models were also adjusted for the related baseline CVD risk with respect to each outcome (e.g. baseline waist in the model of waist changes). Grey shadows show the 95% confidence intervals.