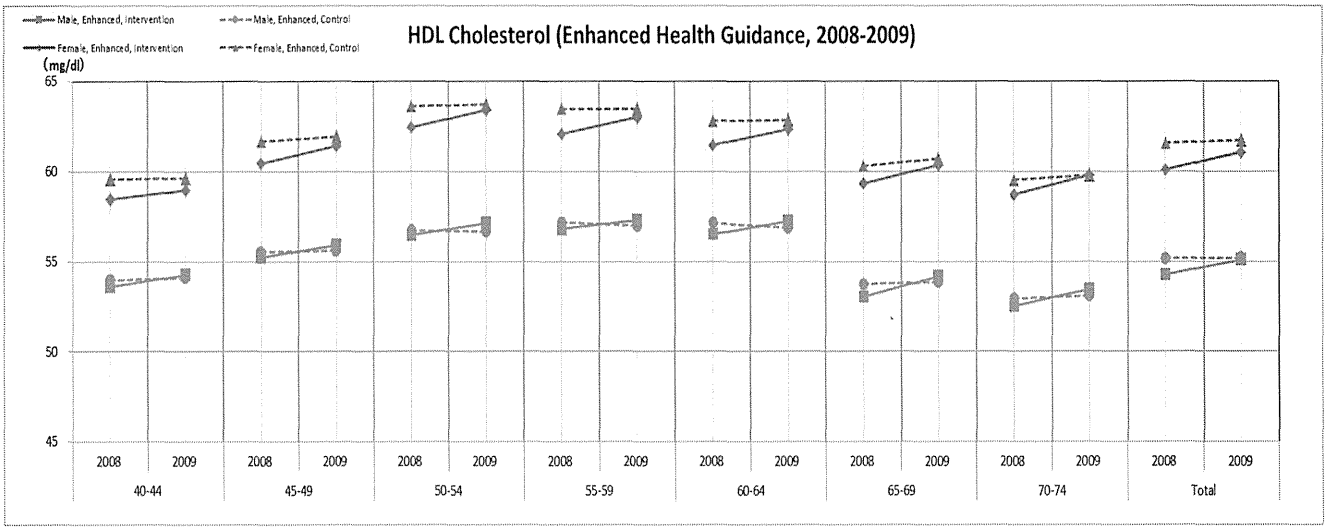
b-9. HDL Cholesterol

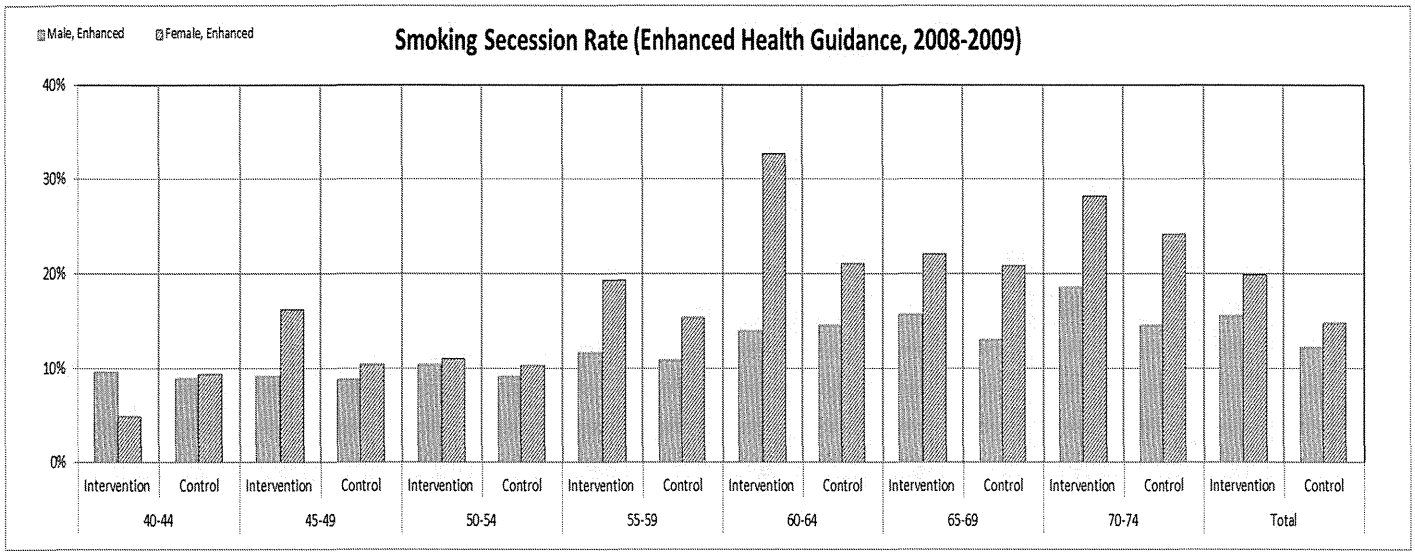


- In the enhanced HG intervention group, HDL cholesterol increased from 54.3mg/dl to 55.1mg/dl (an increase of 0.8mg/dl) in men, and from 60.1mg/dl to 61.1mg/dl (an increase of 1.0mg/dl) in women. (FY 2008-09)

- In the control group, HDL cholesterol increased only by 0.03mg/dl in men and 0.2mg/dl in women. The differences of increases in HDL cholesterol between intervention and control groups were statistically significant for both men (0.8mg/dl) and women (0.8mg/dl). (FY 2008-09)

- Similar trends were observed for FY 2009-10 and FY 2010-11: the differences of changes in HDL cholesterol between intervention and control groups were 0.7mg/dl for men and 0.4mg/dl in women (FY 2009-10), and 0.7mg/dl for men and 0.6mg/dl for women (FY 2010-11). These differences were all statistically significant.

b-10. Smoking Status

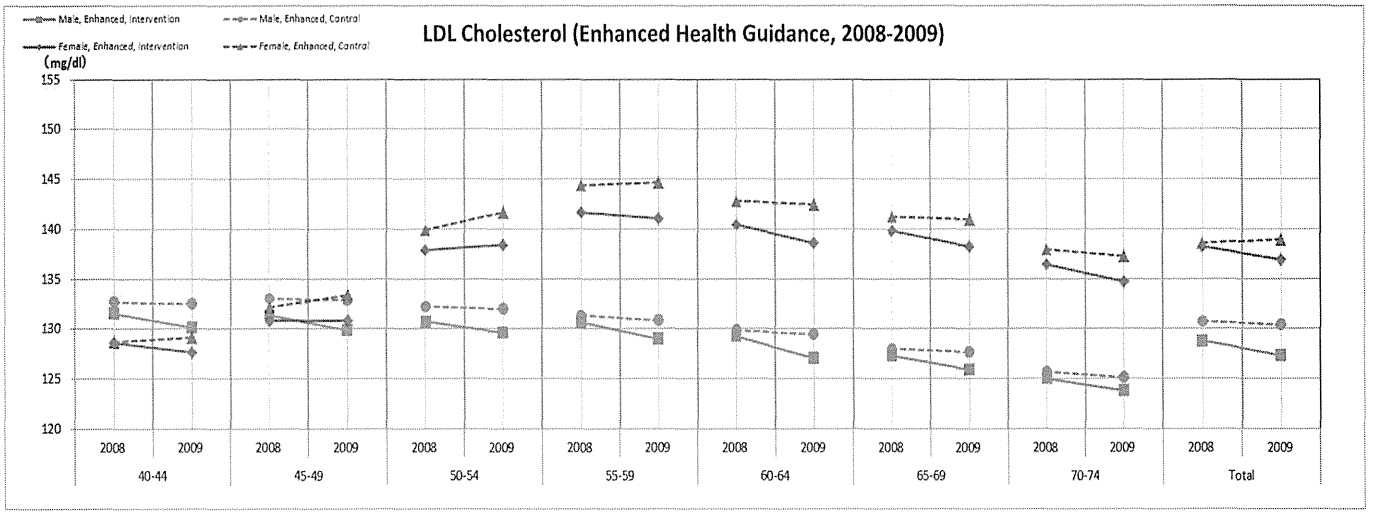


- For smoking status assessment, smoking cessation rates (i.e. percentages of non-smokers in Time 2 among current smokers in Time 1) were assessed. The enhanced HG intervention group generally had higher smoking cessation rates compared to the control group for both men and women in all study years.

- In men in their 40s and 50s, the differences in smoking cessation rates between intervention and control groups tended to be small.

- Similar trends were observed for FY 2009-10 and FY 2010-11

b-11. LDL Cholesterol - additional indicator

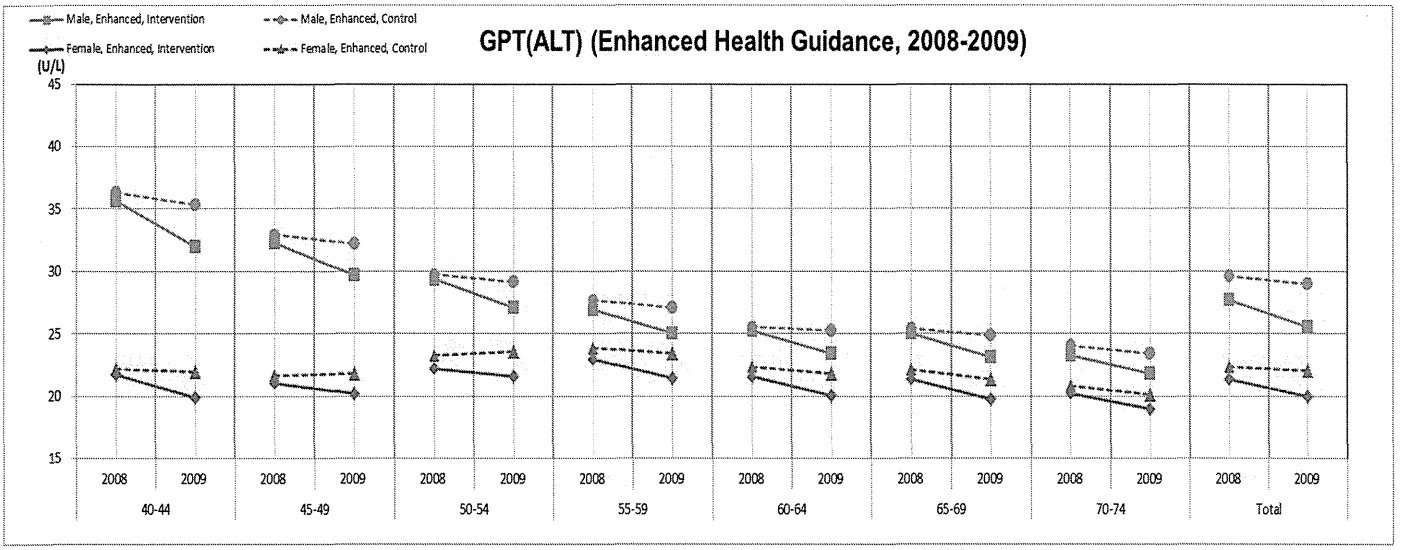


- In the enhanced HG intervention group, LDL cholesterol decreased from 128.8mg/dl to 127.3mg/dl (a decrease of 1.4mg/dl) in men, and from 138.2mg/dl to 136.9mg/dl (a decrease of 1.3mg/dl) in women. (FY 2008-09)

- In the control group, LDL cholesterol decreased by 0.3mg/dl in men but increased by 0.32mg/dl in women. The differences of changes in HDL cholesterol between intervention and control groups were statistically significant for both men (1.1mg/dl) and women (1.6mg/dl). (FY 2008-09)

- Similar trends were observed for FY 2009-10: the differences of changes in LDL cholesterol between intervention and control groups were 1.1mg/dl for men and 1.2mg/dl in women. These differences were all statistically significant.

b-12. ALT (GTP) – additional indicator

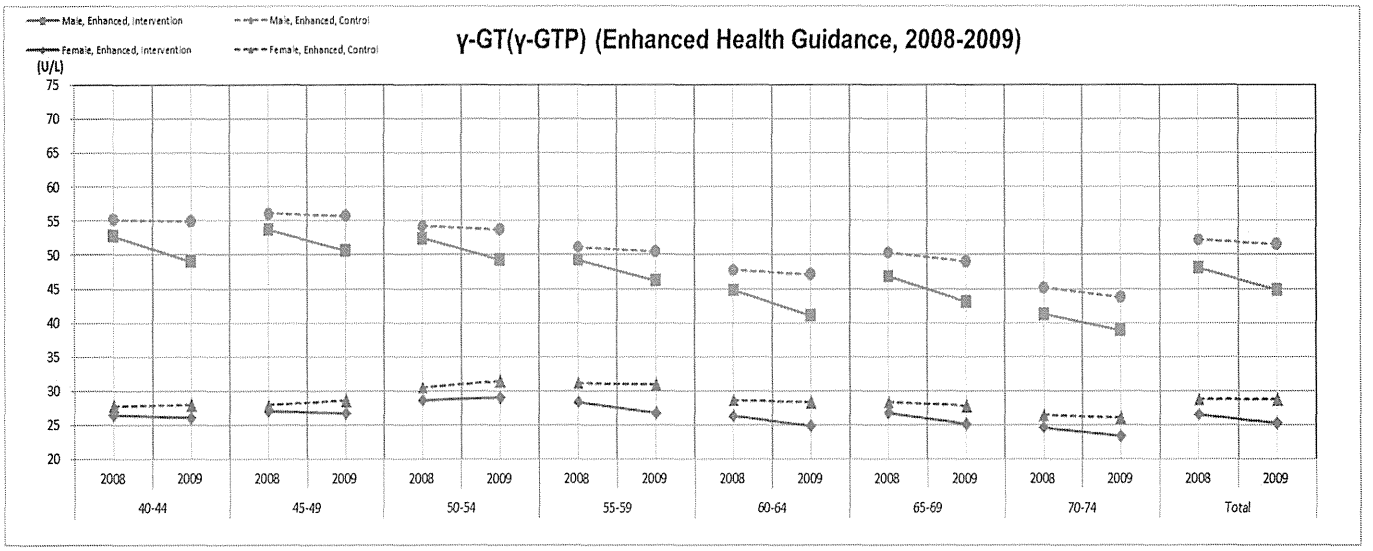


- In the enhanced HG intervention group, ALT decreased from 27.7U/L to 25.5U/L in men (a decrease of 2.2U/L), and from 21.4U/L to 20.0U/L in women (a decrease of 1.4U/L). (FY 2008-09)

- In the control group, ALT decreased only by 0.7U/L in men and 0.3U/L in women. The differences of decreases in ALT between intervention and control groups were statistically significant for both men (1.5U/L) and women (1.1U/L). (FY 2008-09)

- Similar results were found for FY 2009-10 and FY 2010-11: the differences of decrease in ALT between intervention and control groups were 1.2U/L for men and 1.1U/L for women (FY 2009-10), and 0.9U/L for men and 0.7U/L for women (FY 2010-11). These differences were all statistically significant.

b-13. ϒ-GT (ϒ-GTP) – additional indicator



- In the enhanced HG intervention group, ϒ-GT decreased from 48.1U/L to 44.8U/L in men (a decrease of 3.3U/L), and from 26.5U/L to 25.3U/L in women (a decrease of 1.2U/L). (FY 2008-09)

- In the control group, ϒ-GT decreased by 0.7U/L in men but increased by 0.04U/L in women. The differences of changes in ALT between intervention and control groups were statistically significant for both men (2.6U/L) and women (1.3U/L). (FY 2008-09)

- Similar results were found for FY 2009-10 and FY 2010-11: the differences of decrease in ϒ-GT between intervention and control groups were 2.0U/L for men and 1.2U/L for women (FY 2009-10), and 1.5U/L for men and 0.8U/L for women (FY 2010-11). These differences were all statistically significant.

1-4 Discussion – Changes of Clinical and Behavioral Indicators

This study examined the effects of health guidance on clinical and behavioral indicators using the SHEHG Mandate health examination data from FY 2008 to FY 2011. Study subjects were adults 40 to 74 years of age who became eligible to receive intensive or enhanced HG because of elevated metabolic risk factors. Health examination data for baseline (Time 1) and one year later (Time 2) were compared for the intervention group (those who completed HG) and the control group (those who did not participate in HG or dropped out from HG), stratified by type of HG, fiscal year (FY), gender, and age groups.

Overall and for each stratum, the intervention groups achieved greater reductions in waist circumference, BMI, and body weight, and also had greater improvements in blood glucose, blood pressure, and lipid compared to their respective control groups. The magnitudes of improvements however, have become incrementally smaller in each year since 2008. One could argue that this is because highly motivated individuals participated in HG in the initial year, the proportions of less motivated and/or hard-to-improve individuals became higher in later years. Nonetheless, continuous training of health care professionals to improve health guidance technique is warranted.

In terms of the HG's effects on individual obesity-related indicators, waist circumference decreased about 2 to 3cm in the intensive HG group, and about 1 to 2cm in the enhanced HG group. For body weight, men in the intensive HG group achieved 2.5% reduction of baseline weight, and women in the same group achieved 3.3% reduction of baseline weigh in one year. These results are close to, or exceeding the body weight reduction goal of 3.0% for the improvement of metabolic syndrome [1]. Among the enhanced HG group, weight reduction was 1.7% for men and 2.3% in women. The magnitudes of weight reductions in the enhanced HG group were smaller compared to the intensive HG group, but still significantly larger compared to its control group.

In terms of the HG intervention's effects on blood glucose, blood pressure and lipid indicators, the following observations are worth discussing further.

First, in the intensive HG group, there were major cardiovascular risk reductions, including decreases of triglycerides by 25 to 30mg/dl, and reductions of systolic blood pressure by 2 to 4mmHg. The Healthy Japan 21 set a goal to reduce systolic blood pressure by 4mmHg for the entire Japanese population [2]. This study provided evidence that the systolic blood pressure goal can be achieved by lifestyle modification alone.

Second, fasting glucose and HbA1c decreased in both intensive and enhanced HG groups, but increased in their respective control groups. It appears that providing health examination without intervention exacerbates glycemic control in adults who have or are at risk of metabolic syndrome. The enhanced HG was able to stop worsening glycemic control, and the intensive HG actually improved glycemic control. It appears that the modification of lifestyle and reduction of body weight attributed to the HG intervention improved insulin resistance, and also contributed to the prevention of type 2 diabetes.

Lastly, among women in their 50s, LDL cholesterol levels improved among the intervention groups, but worsened in their respective control groups. Menopausal women tend to experience a surge in

HDL cholesterol due to hormonal changes, and so they are more likely to be on medication to control hyperlipidemia [3]. The result of this study suggests that modification of lifestyle can also improve LDL cholesterol in menopausal women.

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[1] A Muratomo, M Matushita, A Kato, N Yamamoto, G Koike, N Nakamura, T Numata, A Tamakoshi, K Tsushita. Three percent weight reduction is the minimum requirement to improve health hazards in obese and overweight people in Japan. Doi.Org/10.1016/j.orcp.2013.10.003

[2] Japanese Ministry of Health, Labor and Welfare. Healthy Japan 21 Resources for the Second Campaign （厚生労働省 「健康日本 21(第二次)の推進に関する参考資料」）
http://www.mhlw.go.jp/bunya/kenkou/dl/kenkounippon21_02.pdf

[3] Comprehensive Survey of Living Conditions (国民生活基礎調査)

2. Changes in Health Guidance Eligibility

Another series of analyses was conducted to examine how adults who had completed health guidance (HG) intervention for the first time fared in the health examination in the following year, by tracking shifts in health guidance eligibility. Health examination data for fiscal year (FY) 2008 through 2011 were used. All analyses were stratified by type of HG, FY, gender and age groups.

2-1 Study Subjects

Inclusion criteria: Adults between 40 to 74 years of age who 1) had health examination in Time 1 (FY 2008, 2009 or 2010), 2) became eligible to receive HG because of elevated metabolic risk factors, 3) completed HG for the first time and received the final outcome evaluation at the end of the 6th month, and 4) had health examination again in the following year (Time 2).

The numbers of study subjects are summarized in **Table 7**.

Table 7. Number of study subjects

Intensive health guidance			
Time 1 to Time 2	Men	Women	Total
FY 2008 – FY 2009	70,610	9,420	80,030
FY 2009 – FY 2010	101,595	10,683	112,278
FY 2010 – FY 2011	134,217	10,333	144,550
Enhanced health guidance			
Time 1 to Time 2	Men	Women	Total
FY 2008 – FY 2009	82,765	48,125	130,890
FY 2009 – FY 2010	105,035	52,942	157,977
FY 2010 – FY 2011	122,509	47,134	169,643

2-2 Statistical Analysis

Analyses focused on changes in eligibility for health guidance from Time 1 to Time 2 among adults who completed HG intervention for the first time in Time 1. All analyses were stratified by type of HG, FY, gender and age groups.

For instance, among adults who completed the intensive HG for the first time, the following year's

health examination can classify them into 4 categories: 1) No health guidance required (denoted as "**Information only** "), because several clinical and behavioral indicators have improved and no longer considered at high risk, 2) **Enhanced HG**, because improvements in some indicators reduced overall metabolic risk factors, 3) **Intensive HG**, because no or little metabolic risk reductions were achieved, and 4) ineligible to health guidance because pharmacological therapy started (denoted as "**Drug therapy**").

(Reference) Participant classification for health guidance eligibility (reprinted)

<table>
<tr><th>Waist circumference/ BMI</th><th>Additional risks (Glucose, Lipid, BP)</th><th>Smoking</th><th>Age 40-64</th><th>Age 65-74</th></tr>
<tr><td rowspan="3">≥85cm (men)
≥90cm (women)</td><td>2 or more risks</td><td>Yes or No</td><td rowspan="2">Intensive HG</td><td rowspan="3">Enhanced HG</td></tr>
<tr><td rowspan="2">1 risk</td><td>Yes</td></tr>
<tr><td>No</td><td>Enhanced HG</td></tr>
<tr><td rowspan="4"><85cm (men)
<90cm (women)
but BMI≥25kg/m²</td><td>3 risks</td><td>Yes or No</td><td rowspan="2">Intensive HG</td><td rowspan="4">Enhanced HG</td></tr>
<tr><td rowspan="2">2 risks</td><td>Yes</td></tr>
<tr><td>No</td><td rowspan="2">Enhanced HG</td></tr>
<tr><td>1 risk</td><td>Yes or No</td></tr>
</table>

The definitions of blood glucose, lipid, and blood pressure risks are as follows:

Blood glucose: Fasting glucose≥100mg/dl or HbA1c≥5.6% by the NGSP unit. If both fasting blood glucose and HbA1c are measured, use the fasting glucose value. Note that HbA1c tests done on or before March 31 2013 are reported in the JDS unit (Japanese standard). HbA1c tests done after March 31 2013 are reported in the NGSP unit (International standard). In this report, all HbA1c values are reported in the JDS unit, and the cutoff value for blood glucose risk is HbA1c≥5.2%.

Lipid: Triglycerides≥150mg/dl or HDL<40mg/dl.

Blood Pressure: Systolic≥130mmHg or Diastolic≥85mmHg

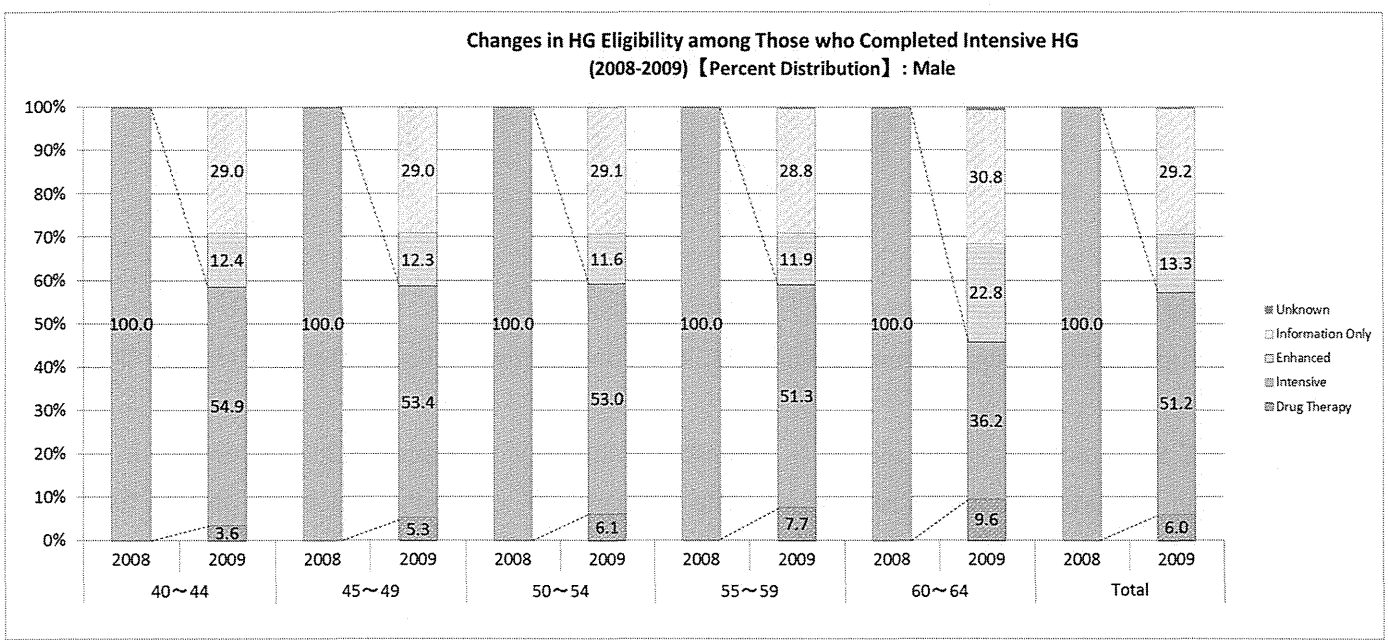
Note: Individuals who are already taking medication for diabetes, hyperlipidemia or hypertension are not eligible for health guidance

2-3 Results

Note: In the result section, all graphs are for the FY 2008-09 data. Other years are described without graphs. All numbers are rounded.

a Intensive HG Intervention vs. Control

a-1. Men



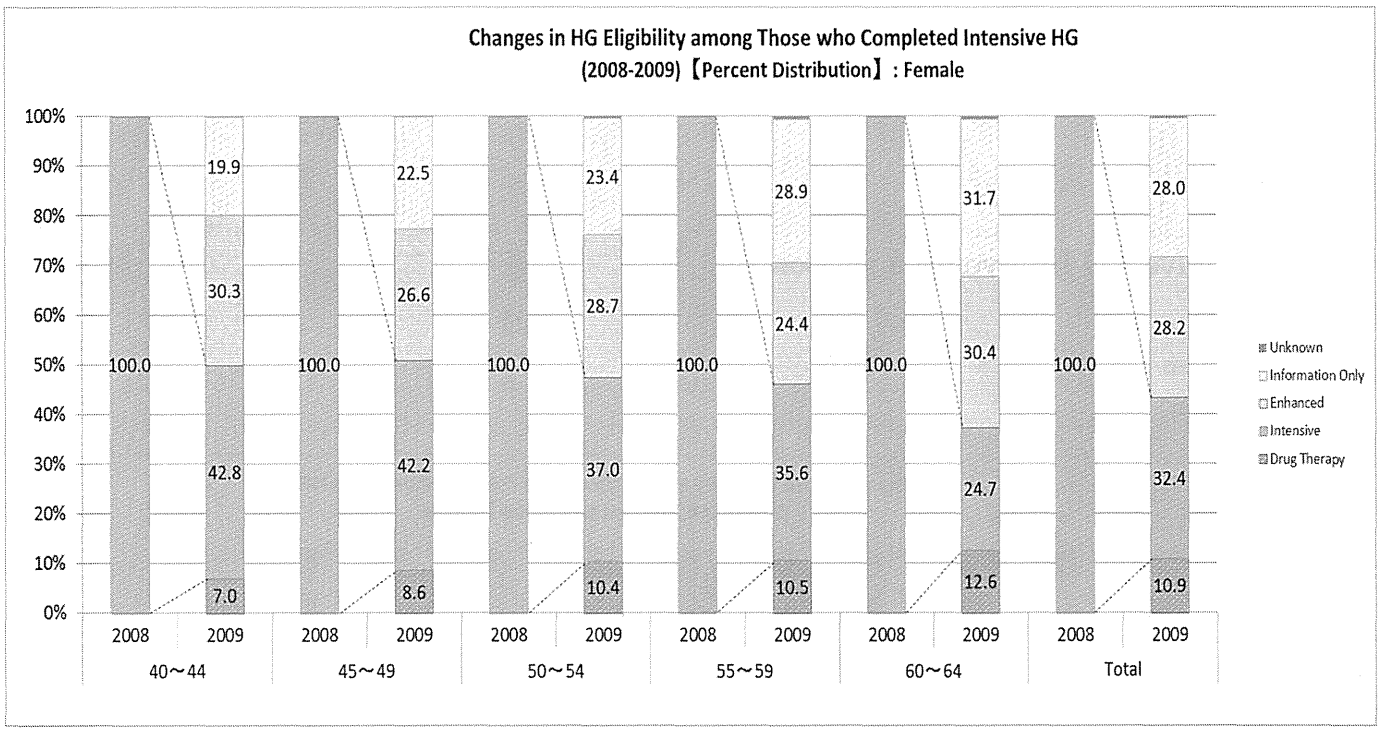
The following sections describe men who completed the intensive HG for the first time in 2008.

- From FY 2008 to 2009, 29.2% moved to the information only category, 13.3% moved to the enhanced HG category, 51.2% remained in the Intensive HG category, and 6.0% shifted to the drug therapy category.

- From FY 2009 to 2010, 25.6% moved to the information only category, 12.6% moved to the enhanced HG category, 55.2% remained in the intensive HG category, and 6.5% shifted to the drug therapy category.

- From FY 2010 to 2011, 22.7% moved to the information only category, 13.2% moved to the enhanced HG category, 57.5% remained in the intensive HG category, and 6.6% shifted to the drug therapy category.

a-2. Women



The following sections describe women who completed the intensive HG for the first time in 2008.

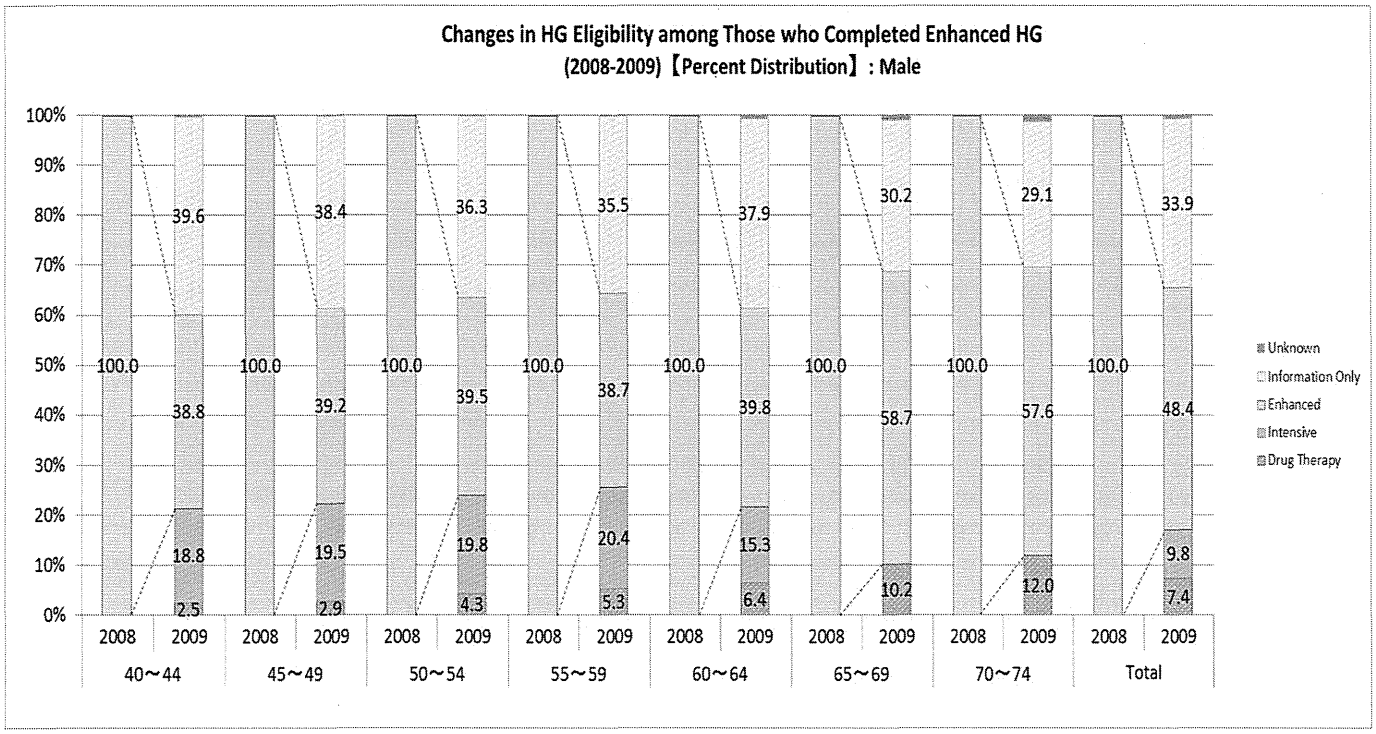
- From FY 2008 to 2009, 28.0% moved to the information only category, 28.2% moved to the enhanced HG category, 32.4% remained in the intensive HG category, and 10.9% shifted to the drug therapy category.

- From FY 2009 to 2010, 23.1% moved to the information only category, 25.7% moved to the enhanced HG category, 39.0% remained in the intensive HG category, and 11.9% shifted to the drug therapy category.

- From FY 2010 to 2011, 19.7% moved to the information only category, 26.0% moved to the enhanced HG category, 43.4% remained in the intensive HG category, and 10.7% shifted to the drug therapy category.

b Enhanced HG Intervention vs. Control

b-1. Men



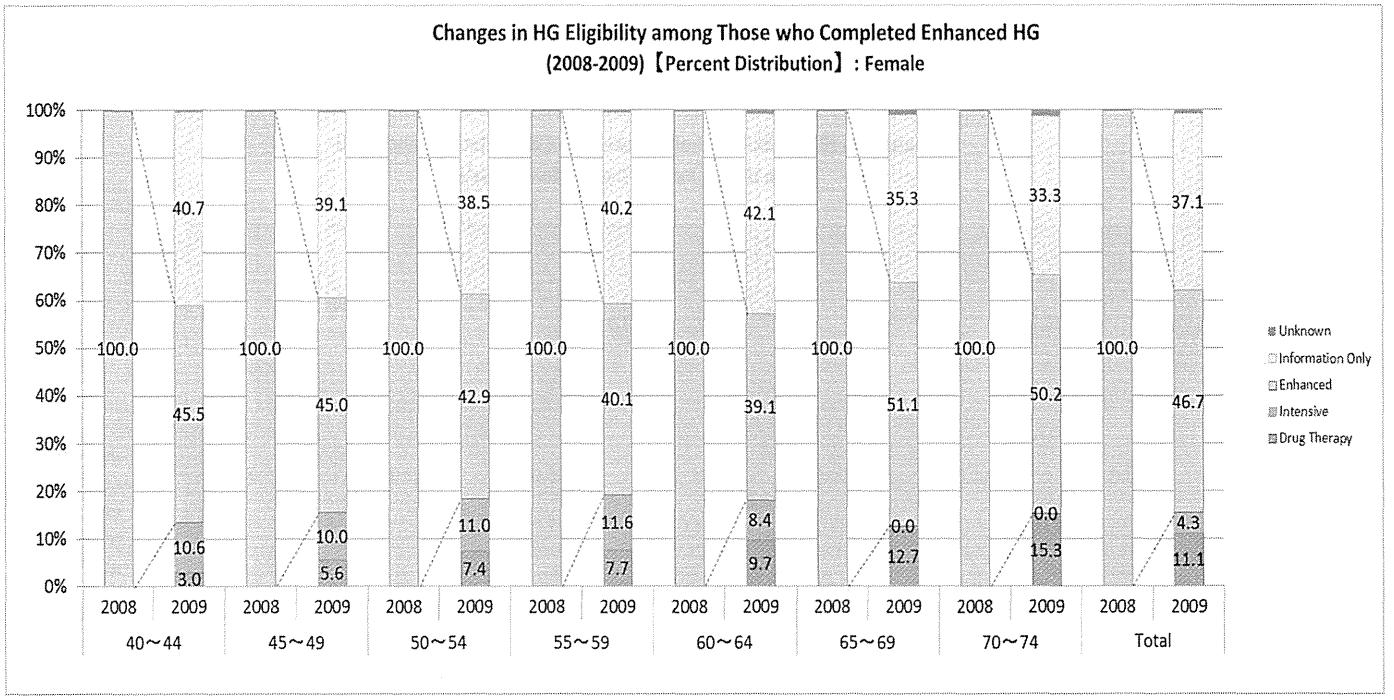
The following sections describe men who completed the enhanced HG for the first time in 2008.

- From FY 2008 to 2009, 33.9% moved to the information only category, 48.4% remained in the enhanced HG category, 9.8% moved to the intensive HG category, and 7.4% shifted to the drug therapy category.

- From FY 2009 to 2010, 31.9% moved to the information only category, 48.7% remained in the enhanced HG category, 12.0% moved to the intensive HG category, and 7.2% shifted to the drug therapy category.

- From FY 2010 to 2011, 31.5% moved to the information only category, 46.9% remained in the enhanced HG category, 15.3% moved to the intensive HG category, and 6.1% shifted to the drug therapy category.

b-2. Women



The following sections describe women who completed the enhanced HG for the first time in 2008.

- From FY 2008 to 2009, 37.1% moved to the information only category, 46.7% remained in the enhanced HG category, 4.3% moved to the intensive HG category, and 11.1% shifted to the drug therapy category.

- From FY 2009 to 2010, 33.4% moved to the information only category, 49.4% remained in the enhanced HG category, 5.6% moved to the intensive HG category, and 11.2% shifted to the drug therapy category.

- From FY 2010 to 2011, 32.9% moved to the information only category, 50.1% remained in the enhanced HG category, 7.3% moved to the intensive HG category, and 9.5% shifted to the drug therapy category.

2-4. Discussion –Changes in Health Guidance Eligibility

The analyses of the shifts of health guidance eligibility before and after intervention revealed that approximately 40% of men and 50% of women who had completed the intensive HG improved their metabolic risk factors in the following year. Furthermore, nearly 20% of those who had completed the intensive HG made large enough improvements to move up to the information only category. On the other hand, about 6% of men and 10% of women who had completed the intensive HG began pharmacological therapy before the following year's health examination.

Among those who had completed the enhanced HG, approximately 30% of men and women saw improvements and moved up to the information only category. However, around 25% of men younger than 65 years of age worsened their metabolic risk factors and moved down to the intensive HG category.

In general, adults who completed the intensive HG tended to move up to a lighter health guidance category, indicating that intensive HG is an effective approach to improve metabolic risk factors. The magnitudes of improvements tended to be larger in women than in men, most likely because women achieved greater reductions in body weight than men. The fact that women's waist circumference cut-off (90cm) being 5cm larger than men's cut-off (85cm) may have played a role in their greater body weight reductions. In terms of age differences, the positive effects of the intensive HG were seen uniformly in all age groups.
With regard to the enhanced HG, while some achieved improvements in their metabolic risk factors, a similar proportion of others got worse, suggesting a need to improve the enhanced HG curriculum.

For both types of HG, the magnitudes of improvements tended to become incrementally smaller over the years, suggesting that highly motivated individuals might have participated in HG as soon as they become eligible and improved quickly, while less motivated and/or hard-to-improve individuals gradually became over-represent as years pass by. Continuous training of health care professionals to improve HG technique is warranted.

Finally, data for individuals who did not participate or dropped out from HG were not analyzed. In order to show the true effects of HG, comparisons between intervention and control groups are needed. It is important to note that not all the metabolic risk improvements seen in this study were attributed to the HG intervention, because a small proportion of individuals in the control groups were believed to have similar improvements without intervention.

3. Changes in Metabolic Syndrome Status

The last series of analyses was to evaluate the extent of changes in metabolic risk factors in adults who had completed health guidance (HG) intervention for the first time, using the existing metabolic syndrome diagnostic criteria. Health examination data for fiscal year (FY) 2008 through 2011 were used. All analyses were stratified by type of HG, FY, gender and age groups.

3-1 Study Subjects

Inclusion criteria: Adults between 40 to 74 years of age who 1) had health examination in Time 1 (FY 2008, 2009 or 2010), 2) became eligible to receive HG because of elevated metabolic risk factors, 3) completed HG for the first time and received the final outcome evaluation at the end of the 6th month, and 4) had health examination again in the following year (Time 2).

The numbers of study subjects are summarized in **Table 8**.

Table 8. Number of study subjects

Intensive health guidance			
Time 1 to Time 2	Men	Women	Total
FY 2008 – FY 2009	70,771	9,469	80,240
FY 2009 – FY 2010	101,772	10,708	112,480
FY 2010 – FY 2011	134,434	10,354	144,788
Enhanced health guidance			
Time 1 to Time 2	Men	Women	Total
FY 2008 – FY 2009	83,082	48,275	131,357
FY 2009 – FY 2010	105,255	53,075	158,330
FY 2010 – FY 2011	122,832	47,218	170,050

3-2 Statistical Analysis

Analyses focused on changes in group designations based on metabolic syndrome diagnostic criteria from Time 1 to Time 2 among adults who completed HG intervention for the first time in Time 1. All analyses were stratified by type of HG, FY, gender and age groups.

Evaluation of health examination results can classify individuals into three groups 1) The metabolic syndrome (**Met S**) group, 2) pre-metabolic syndrome (**Pre-Met S**) group, and 3) no metabolic

syndrome (**no Met S**) group.

The metabolic syndrome diagnostic criteria used in this study were the criteria based on the joint consensus statement published in April 2005 by eight major Japanese medical organizations, including the Japanese Society of Internal Medicine. The details of the diagnostic criteria are shown in **Table 9**.

Table 9. Japanese metabolic syndrome diagnostic criteria

Waist circumference	Additional risks (Glucose, Lipid, BP)	Diagnosis
≥85cm (men) ≥90cm (women)	2 or more risks	Metabolic syndrome
	1 risk	Pre-Metabolic syndrome

The definitions of blood glucose, lipid, and blood pressure risks are as follows:

Blood glucose: Fasting glucose≥110mg/dl

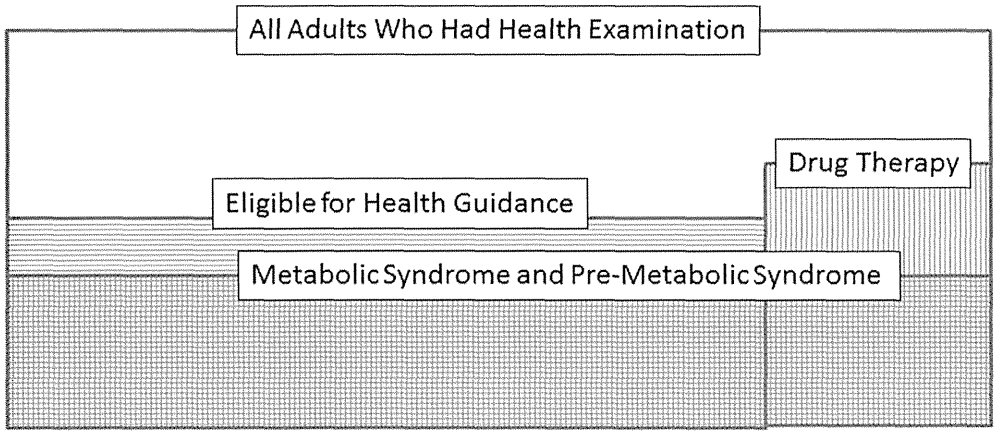
Lipid: Triglycerides≥150mg/dl or HDL<40mg/dl

Blood Pressure: Systolic≥130mmHg or Diastolic≥85mmHg

Note: Individuals who are already taking medication for diabetes, hyperlipidemia or hypertension are also considered at risk

There are notable differences between the Japanese metabolic syndrome diagnostic criteria and the algorithm used to determine HG eligibility (also see the visualization chart below):

- The HG eligibility algorithm excludes those who are on pharmacological therapy
- The HG eligibility algorithm includes the following as metabolic risk factors
  BMI≥25kg/m^2
  Fasting glucose 100-109mg/dl
- The HG eligibility algorithm used smoking status and age for determining HG type



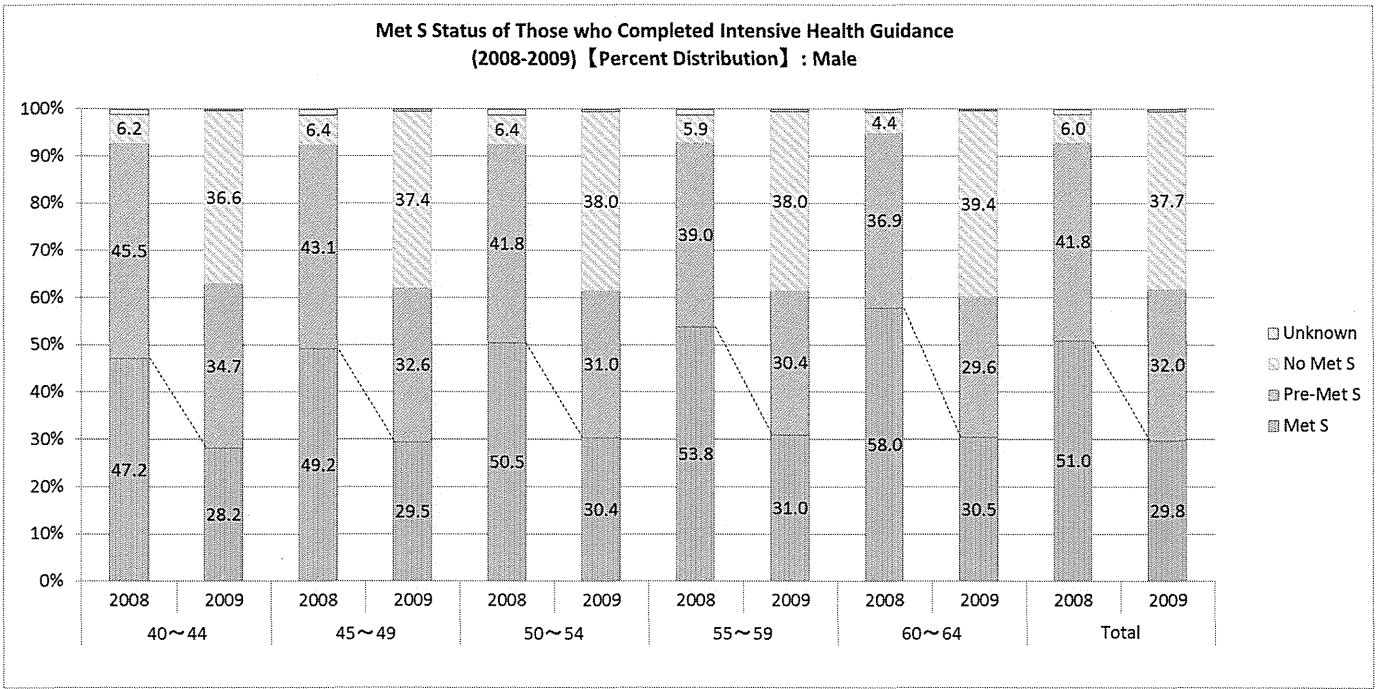
Also note that the Japanese metabolic syndrome diagnostic criteria are also different from the WHO criteria or the NCEP-ATPIII criteria.

3-3 Results

Note: In the result section, all graphs are for the FY 2008-09 data. Other years are described without graphs. All numbers are rounded.

a Intensive HG Intervention vs. Control

a-1. Men



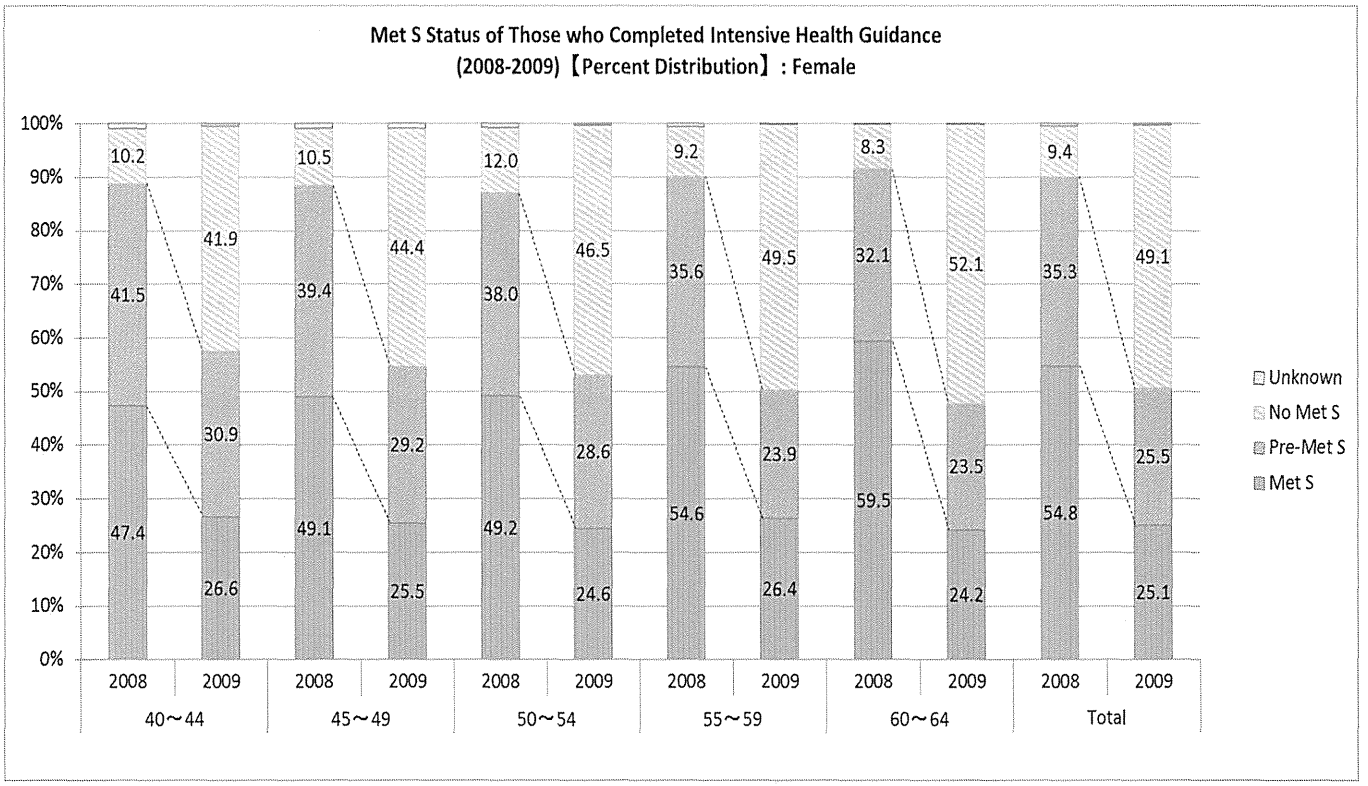
The following sections describe men who completed the intensive HG for the first time in Time 1.

- From FY 2008 to 2009, the Met S group dropped from 51.0% to 29.8%, and the pre-Met S group also decreased from 41.8% to 32.0%. The no Met S group jumped from 6.0% to 37.7%.

- From FY 2009 to 2010, the Met S group decreased from 49.8% to 33.1%, and the pre-Met S group also decreased from 43.7% to 32.8%. The no Met S group increased from 6.3% to 34.0%.

- From FY 2010 to 2011, the Met S group decreased from 49.0% to 34.7%, and the pre-Met S group also decreased from 44.0% to 34.4%. The no Met S group increased from 6.8% to 30.7%

a-2. Women



The following sections describe women who completed the intensive HG for the first time in Time 1.

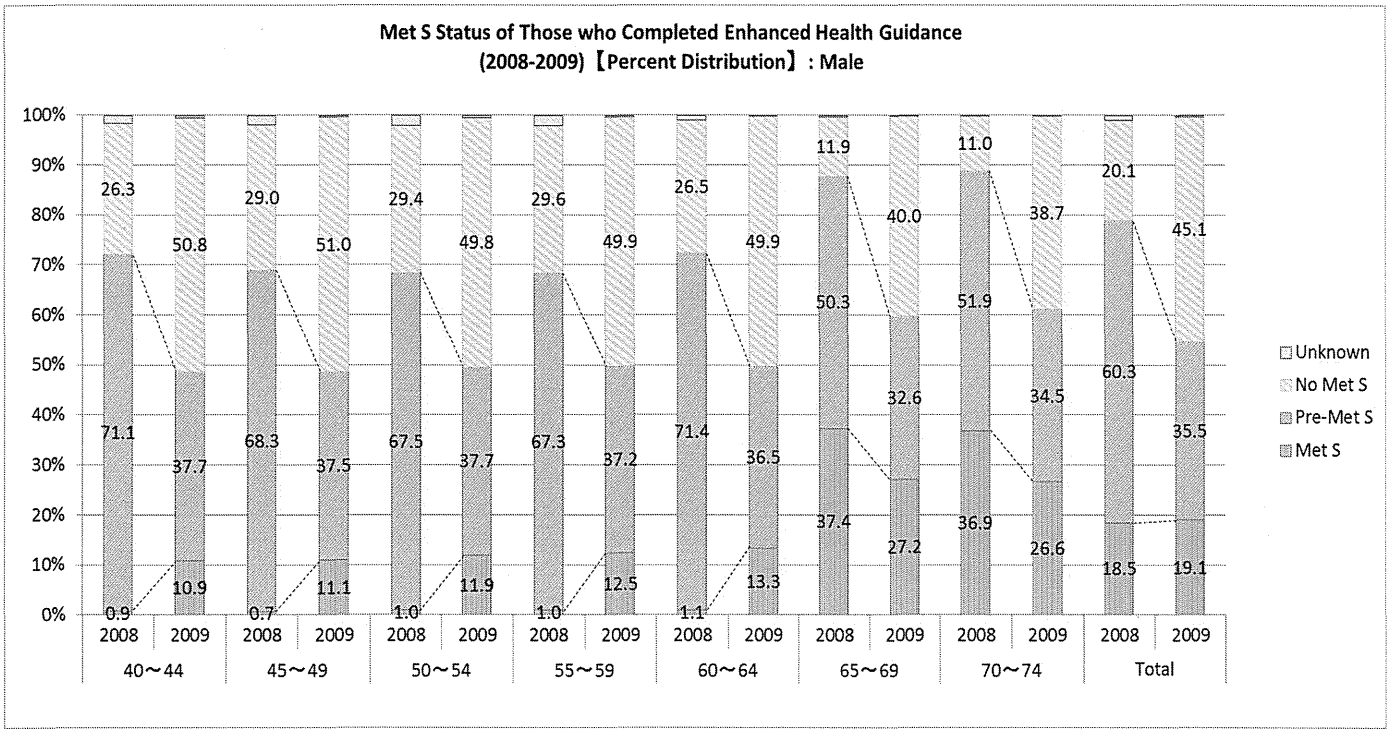
- From FY 2008 to 2009, the Met S group dropped from 54.8% to 25.1%, and the pre-Met S group also decreased from 35.3% to 25.5%. The no Met S group jumped from 9.4% to 49.1%.

- From FY 2009 to 2010, the Met S group decreased from 52.9% to 29.1%, and the pre-Met S group also decreased from 35.7% to 27.2%. The no Met S group increased from 11.3% to 43.7%.

- From FY 2010 to 2011, the Met S group decreased from 50.9% to 30.6%, and the pre-Met S group also decreased from 37.0% to 29.4%. The no Met S group increased from 11.9% to 39.8%.

b Enhanced HG Intervention vs. Control

b-1. Men



The following sections describe men who completed the enhanced HG for the first time in Time 1.

- From FY 2008 to 2009, the Met S group increased slightly from 18.5% to 19.1%, but the pre-Met S dropped from 60.3% to 35.5%. The no Met S group increased from 20.1% to 45.1%.

- From FY 2009 to 2010, the Met S group increased from 14.9% to 19.1%, but the pre-Met S group decreased from 62.0% to 36.4%. The no Met S group increased from 23.1% to 44.3%.

- From FY 2010 to 2011, the Met S group increased from 9.2% to 16.8%, but the pre-Met S group decreased from 63.3% to 38.5%. The no Met S group increased from 27.2% to 44.4%.