Weight change and changes in the metabolic syndrome as the French population moves towards overweight: the D.E.S.I.R. cohort.

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Summary

Background: How weight change affects the metabolic syndrome (MS) and its parameters is unknown, particularly in a leaner European population, such as the French prospective D.E.S.I.R. cohort.

Methods: In 3770 D.E.S.I.R. participants (sex ratio=1) averaging 47.5 years (range 30-64), with measured weight and MS parameters at baseline (D0) and at six-year follow-up (D6), we assessed this relationship across five weight-change classes, using stable weight as the referent group (-2kg to +2kg). We used analysis-of-covariance to assess changes in each MS parameter and logistic regression to assess incident MS, according to the National Cholesterol Education Program (NCEP). We also assessed weight-change effect on MS status between D0-D6.

Results: At D0, average weight was 68.4kg (SD 12.3); BMI was 24.8kg/m2 (SD 3.5). From D0-D6, the cohort gained a mean 2.1kg (median 2.0; SD 4.4). After adjustment for age and D0 weight, there was a strong linear relationship with weight change and worsening of the following MS parameters at D6: fasting insulin, waist girth, fasting glucose, fasting triglycerides, HDL cholesterol, systolic and diastolic blood pressure ($p < 0.0001$). After age adjustment, for every *kilogram* gained over six years, risk of developing the NCEP Syndrome increased 22% (OR 1.22; 95% CI 1.18-1.25). NCEP-MS was incident in 3% of those with stable weight compared to 21% among those gaining >9kg; 10% of those who lost >2kg reverted to non-NCEP-MS.

Conclusions: All continuous MS measures are linearly related to weight change, and MS can resolve with modest weight loss, underscoring the importance of maintaining life-long normal weight.

Keywords: Metabolic Syndrome; Weight Gain; Weight Change; Insulin Resistance,

Abbreviations: MS, metabolic syndrome; OR, odds ratio; CI, confidence interval;

Although self-reported weight gain is strongly associated with onset and development of the metabolic syndrome,[1] we are not aware of any study that has prospectively evaluated the effect of documented weight gain on carefully measured metabolic syndrome parameters. Of particular public health value is to prospectively evaluate the metabolic impact of early weight gain among a normal weight population. Moreover, although strong evidence exists among obese Americans that intentional weight loss reduces future mortality,[2,3] only a few small retrospective case series in morbidly obese persons have evaluated the impact of marked weight loss on individual parameters of the metabolic syndrome.[4,5]

Thus, the impact of moderate weight loss is unknown. In the current study, we prospectively evaluated the effect of weight change (both gain and loss) on parameters of the metabolic syndrome among the French D.E.S.I.R. cohort (Data from an Epidemiological Study on the Insulin Resistance syndrome), which had on-average normal weight at baseline. A secondary aim was to determine the impact of this weight change on change in the presence or absence of the syndrome itself, and the risk of incident metabolic syndrome.

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Methods

Study Population. D.E.S.I.R. is a longitudinal cohort study of 5,212 adults aged 30-64 years at baseline with the primary aim of describing the natural history of the metabolic syndrome. Subjects were recruited from 1994-6 from 10 different Social Security Health Examination centers in western-central France, among volunteers insured by the French national social security system (80% of the French population – any employed or retired person and their dependents which offers free periodic health examinations. As part of the recruitment design, men and women were recruited equally among five-year age groups. . All subjects gave written informed consent, and the study protocol was approved by the CCPPRB (Comité Consultatif de Protection des Personnes pour la Recherche Biomédicale) of Hôpital Bicêtre (Paris, France). There were 4,111 participants that attended the six-year follow-up exam.

We evaluated the relation of weight change with the metabolic syndrome over six years among the participants who had measured weight, height, weight circumference, blood pressure, and the following *fasting* measurements at both baseline and six-year follow-up: glucose, insulin, triglycerides, and HDL cholesterol (3,843 participants had fasting samples and all of these MS measures at both exams). Participants who were underweight (BMI <18.5 kg/m2)[6] were excluded (n=73) because of potential confounding with parameters due to illness, leaving a final study sample of 3,770.

Biological, anthropometric, and clinical measurements. Venous blood samples were collected after a 12-hour fast. Serum insulin was quantified by MEIA (Micro particle Enzyme Immunoassay) with the IMX automated analyzer from Abbott, Rungis, France, and plasma glucose was assessed by enzymatic method (modified glucose oxydase peroxydase) using a Technicon RA 1000 automated analyzer from Bayer Diagnostics, Puteaux, France, or a Specific or a Delta from Konelab, Evry, France. Serum HDL-cholesterol and serum triglycerides were assayed respectively by phosphotungstic precipitation method and enzymatic Trinder method, using a Technicon DAX24 automated analyzer from Bayer Diagnostics, Puteaux, France, or a Specific or a Delta from Konelab, Evry, France. There

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were four laboratories for the 10 study centers, which maintained an inter-laboratory quality control for comparability of the biologic data. Seventy percent of the subjects had biochemical analyses in one laboratory. Subjects returned to the same health center laboratory for their health examination six years after inclusion. Insulin was measured centrally in one laboratory.

Anthropometric measures were done according to a standard manual of procedures for the D.E.S.I.R. study by trained personnel with the same methods at both the D0 and D6 exams. A nurse or doctor measured height with a stadiometer (without shoes), weight (in light clothes), waist circumference with a tape measure (the smallest circumference between lower ribs and iliac crests), systolic and diastolic blood pressure at rest (at least 5 minutes) in a supine position on the right arm using a mercury sphygmomanometer. Two blood pressure measurements were taken at five-minute intervals, and we used the average of the two. Alcohol use, smoking, and physical activity were assessed by questionnaire. Smoking was dichotimized (yes/no). As the majority of persons drank alcohol and participated in regular daily sporting activities, based on their distributions, we classified alcohol use as none, 1-20 grams per day, and >20 grams per day; sporting activity was classified as none, once weekly, and more than once weekly.

Metabolic syndrome was defined as per the National Cholesterol Education Program (NCEP),[7] by presence of three or more of the following possible five criteria: (a) fasting plasma glucose (FPG) $\geq$6.1 mmol/L; (b) waist circumference >88 cm (women) or >102 cm (men); (c) blood pressure $\geq$130/85 mmHg; (d) triglycerides $\geq$1.69 mmol/L or (e) HDL cholesterol <1.29 mmol/L (women) or <1.04 mmol/L (men).

Weight Change. Based on the distribution of weight change both overall and among both sexes, we divided six-year weight change into five groups that were clinically meaningful: (1) Weight Loss (< -2 kg); (2) Weight Stable Referent Group (- 2 kg to + 2 kg); (3) Mild Weight Gain (+ 3 to 5 kg); (4) Moderate Weight Gain (+ 6 to 8 kg); and (5) Large Weight Gain ($\geq$ + 9 kg). To facilitate interpretation of weight change, we evaluated absolute rather than percent weight change among this population with

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an average normal weight at baseline, and thus the range of baseline weight was narrower than many other populations.

Statistical methods. All statistical analyses were performed with the SAS V8 System® (SAS Institute, Inc., Cary, North Carolina, USA). Paired t-tests and chi-squared tests were used to compare changes in means and proportions, respectively between baseline and follow-up.

General Linear Models were used to estimate the adjusted means of the individual MS parameters at the six-year exam (D6) according to the weight-change group, and adjusting for the corresponding MS parameter at D0, rather than evaluating absolute change as the outcome. This has higher statistical power to evaluate change over time.[8,9] We also adjusted every model for age, and baseline weight (to account for size differences), after verifying that weight change was not significantly correlated with baseline weight (Spearman r= -0.01; p=0.5 for the entire population). Thus, using insulin as an example, each of the metabolic syndrome parameters were modeled as follows: D6Insulin=D0Insulin + age + baseline weight + weight change (in the 5 classes above). We also assessed the overall trend of weight change across classes. Linear and non-linear models were tested, and we also tested for an interaction between age and weight change with each of the individual components of the syndrome. We evaluated the effects of smoking, alcohol use, physical activity, and unintentional weight loss on the relationship of weight change and change in metabolic syndrome (MS) parameters.

We then assessed the impact of a 1kg weight change on incident MS. We further studied the relations between weight change groups and the status of the MS at D0 and D6 during the six-year follow-up: (1) Remaining Stable and Normal (no MS at D0 or D6); (2) Reversion to Normal (MS at D0 but NOT at D6); (3) Incident MS (Normal at D0 but MS present at D6); and (4) Remaining Stable in Abnormal Range (MS present at both D0 and D6).

Results

At baseline, the average BMI was 24.8 kg/m^2 (median 24.0, SD 3.5) among the 3,770 men and women with an average age of 47.5 years (SD 9.9) and the average weight was 68.4 kg (SD 12.3) with a range of 43-119 kg which was symmetrically distributed. At baseline, 58% of the 3,770 participants were normal weight (BMI 18.5-24.99 kg/m^2), 33% were overweight (BMI 25-29.99 kg/m^2), and 9% were obese (BMI>30 kg/m^2). There were expected differences by sex in both size and metabolic syndrome parameters (Table 1). After six years of follow-up, the cohort gained a mean weight of 2.1 kg (median 2.0; SD 4.4) with a range of –20 to +34 kg of weight change, and overweight had increased to 38%; 13% were obese. Weight change was similar in men and women (Table 1). Furthermore, when weight change was stratified by baseline normal weight (BMI 18.5-24.99 kg/m2), overweight (BMI 25-29.99 kg/m2), and obese (BMI $\geq$ 30 kg/m2), the mean weight change was remarkably similar among all three baseline BMI groups (data not shown). In addition to an average weight gain of 2.1 kg, there was a worsening in all of the syndrome parameters on average, except for HDL cholesterol in women over the six-year follow-up (Table 1).

Weight Change and Change in the Metabolic Syndrome Parameters

There was a strong linear trend with increasing weight gain and worsening of all the metabolic syndrome parameters among both men and women (Table 2). As the significance of this worsening was p<0.0001 for all parameters, we also noted the F-value for weight change in each model that was similarly adjusted for age, baseline weight, and the baseline parameter. An F-value of $\geq$ 4.62 for the weight-change variable (with 4 degrees of freedom) in our sample is equal to a p-value of <0.001,[10] and a F-value $\geq$ 5.90 a p-value <0.0001. However, there was still a marked range in F-values over 5.90, with glucose and blood pressure among the smallest for men and women (F=8-11), insulin the second largest (F= 52-61) and not surprisingly, waist girth with an F-value >240 (Table 2). Furthermore, insulin levels had the greatest proportional change across the weight change groups (Table 2). Both insulin and triglycerides had a distribution skewed towards the right (higher values), and models with log-transformed insulin and triglycerides showed similarly significant results (not shown). Moreover,

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absolute insulin values nearly doubled across the weight change groups for both men and women (Table 2). These relationships remained highly significant even with adjustment for change in waist circumference (data not shown).

Reported smoking, alcohol use, and sports activity showed similar frequencies across most weight change classes in men and women, except for those with marked weight gain ($\geq$ 9 kg), who were more likely to be smokers, non-drinkers, and less active on univariate analyses (p<0.01 for each, data not shown). Therefore, we did additional models evaluating associated change in the individual syndrome parameters across weight change groups which also adjusted for self-reported frequency of daily smoking and alcohol use and weekly sports activities. Adjusted means for each of the metabolic syndrome parameters reported in Table 2 were unchanged after these adjustments (data not shown). We also did further analyses restricted to non-smokers and found similar results.

Table 1 shows the prevalence of drug treatment for diabetes, hypertension, and hyperlipidemia at the baseline and six-year visits in the population. As it is possible that medication use could affect the relation between weight gain and MS parameters, we also did separate analyses restricted to subjects non-treated for the relevant parameters (i.e.restricting to no self-reported treatment with hypoglycemic medications for measured glucose, no self-reported treatment for hypertension for blood pressure measurements, and no self-reported treatment for hyperlipidemia for the lipid measurements); results were unchanged with these restrictions (data not shown). Finally, among the weight loss group, restricting analyses to only those who reported trying to lose weight also revealed similar improvement in MS parameters as that seen among the entire weight loss group.

Weight Change and the Change in the Metabolic Syndrome

After adjustment for age, for every *kilogram* weight gained over the six-year period, the risk of developing the NCEP Syndrome increased 22%, and this risk was the same for both men and women (overall OR 1.22; 95% CI 1.18-1.25). Increasing weight gain was associated with higher rates of both developing and maintaining the syndrome (if it was present at baseline). Just as importantly, reversion

to normal among those who had the syndrome at baseline was much more frequent among those who lost weight (p<0.0001, Figure 1).

Discussion

In this prospective cohort that was established *a priori* to study the natural history of the metabolic syndrome, we found a strong linear relationship with weight gain and worsening of each of the continuous measures that constitute the metabolic syndrome. This strong relationship was present after adjustment for age and initial weight. Furthermore, the frequency of the metabolic syndrome (both development and improvement) was strongly associated with weight change.

There are surprisingly few prior studies of weight gain and the MS, particularly measured changes in its parameters. One cross-sectional study of Finnish middle-aged men found that weight gain, based on self-reported weight at age 20, was associated with increased risk of developing the insulin resistance syndrome.[1] The U.S. CARDIA cohort of young adults (mean age 24 years) found that both BMI and weight gain were independently associated with incident NCEP syndrome. Conversely, although strong evidence exists among obese Americans that intentional weight loss reduces future mortality,[2,3] only a few small retrospective case series in morbidly *obese* persons have evaluated the impact of marked weight loss on individual parameters of the metabolic syndrome.[4,5]

To best understand how to alter the course of our worldwide obesity and resultant Type 2 diabetes epidemic,[6,11-13] it is important to evaluate it as it begins. France has the lowest prevalence of obesity among nine Northern European countries,[14] and among the lowest of Westernized countries in the world.[15] However, there are now beginning signs of increasing obesity within France as well, in both adults and children.[16-19] Thus, our D.E.S.I.R. cohort in central France provides an opportunity to evaluate the beginning of the obesity epidemic, and the pathogenesis of early weight gain in a previously normal weight population.

We found that there was a strong linear relationship with weight gain and each of the MS parameters (p<0.0001). Moreover, there was a range of F-values above the 5.90 range (p<0.0001 for

Supprimé : 17/11/05

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our model), with insulin being the second highest F-value after waist girth for both men and women (F=52-61), triglycerides and HDL cholesterol an intermediate F-value, and glucose and blood pressure closer to the 5.90 cut-off (F=8-11; see Table 2). This strong linear relationship with weight gain and worsening of all MS parameters remained even after adjustment for change in waist girth (p<0.0001). Moreover, the F-value remained the highest by a similar ratio for insulin for both men and women (compared to triglycerides, HDL, systolic and diastolic blood pressure, and glucose; data not shown). The recognition that insulin is central to the metabolic syndrome is not new information, and in fact the metabolic syndrome is also termed the "insulin resistance syndrome".[20,21] However, we are not aware of any prior population-based study that has evaluated the differing physiologic changes of early weight gain on the syndrome. Moreover, the strongest linear association with insulin (after waist girth) is important new information from a public health perspective as our results demonstrate that even mild weight gain is associated with notably increased hyperinsulinaemia.

As illustrated with Figure 1, these physiologic changes translate into both a higher prevalence of the metabolic syndrome (with weight gain), and increased reversion to normal (with weight loss) (p<0.0001 for each NCEP category trend across weight change groups). We used the original NCEP definition[7] of a measured fasting glucose (FPG) abnormality $\geq$ 6.1-6.99 mmol/L rather than the revised American Diabetes Association criteria of an impaired fasting glucose (IFG) of $\geq$ 5.6 mmol/L,[22] as the higher threshold for IFG has a stronger association with risk of diabetes and cardiovascular disease than the revised ADA criteria.[23,24] However, we also assessed the relationship with weight change and the NCEP syndrome, using FPG $\geq$ 5.6 mmol/L as the criteria, and found a similarly strong relationship with both increasing incidence of NCEP syndrome with weight gain and reversion to normal with weight loss (data not shown).

As our purpose was to study the population effect of weight change on the physiology of the metabolic syndrome, we analyzed both metabolic syndrome parameters and the syndrome itself irrespective of treatment. If anything, this would attenuate the relationship we observed. Importantly, even with separate analyses restricted to those untreated for diabetes, hypertension, or

Supprimé : 17/11/05

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hypercholesterolemia, the linear relationship with weight gain and worsening of the respective syndrome parameters remained.

There was a strong *inverse* linear trend with increasing weight gain and reverting to not having the NCEP syndrome (improving) during follow-up (p<0.0001 for trend; Figure 1). However, 37 people (2%) who gained ≥ 3 kg still reverted to no NCEP syndrome. There was no significant difference in the proportion of persons initiating medication treatment across all weight change groups, so initiation of medication is an unlikely explanation for reversion to no NCEP syndrome among those that gained weight. Other possibilities include intensification of either continuing medication or physical activity— which we cannot accurately assess—or regression to the mean.

Our study is limited in that not all participants who presented at the baseline exam attended subsequent examinations. However, comparing those lost to follow-up with those present at the six-year follow-up exam, we found no significant difference between baseline mean weight, BMI, or waist circumference. Thus significant bias from loss to follow-up is unlikely.

In summary, among a community-dwelling population of middle-aged adults recruited to prospectively study the metabolic syndrome, we found a strong linear continuous relationship with each physiologic continuous measure of the metabolic syndrome, as well as development of the syndrome itself. Just as importantly for public health, increasing reversion to normal (absence of the syndrome) was seen among those with weight stability, and more so in those with weight loss. Our results support increased and vigorous public health efforts to maintain normal life-long weight. Weight maintenance/loss campaigns offer an economical and benign approach to ameliorate the magnitude of health and health care consequences threatened by the growing worldwide obesity and Type 2 diabetes epidemic.

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LEGEND FOR FIGURE

Figure 1: Association between Weight Change and Presence (+) or Absence (-) of the metabolic syndrome (MS) among 3,770 D.E.S.I.R participants between baseline (D0) and the six-year follow-up exam (D6). Increasing weight gain was linearly related with both incident and continued MS (p<0.0001 for each trend) and inversely related with the proportion either remaining stable without MS or reverting to absence of MS (p<0.0001 for each trend).

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Table 1. Characteristics of the metabolic syndrome parameters among 3,770 participants in the D.E.S.I.R. (
exam (D0) and 6-year follow-up exam (D6) by sex

Characteristic	Men (n=1,870)			Women (n=1900)	
	D0	D6	p-value (D0 vs. D6)	D0	D6
Age, years	47.4 (9.9)	53.4 (9.9)	--	47.6 (9.9)	53.6 (9.9)
Weight, kg	75.6 (10.2)	77.5 (11.1)	<0.0001	61.4 (9.9)[†]	63.7 (11.0)[†]
BMI, kg/m^2	25.4 (3.1)	26.0 (3.4)	<0.0001	24.2 (3.8)[†]	25.2 (4.3)[†]
Waist girth, cm	89.4 (9.0)	91.6 (9.6)	<0.0001	77.3 (9.8)[†]	80.5 (11.2)[†]
FPG[‡], mmol/L	5.5 (0.8)	5.6 (0.9)	0.008	5.1 (0.7)[†]	5.2 (0.7)[†]
Insulin, pmol/l	47.3 (31.4)	56.5 (39.2)	<0.0001	44.5 (24.9)[*]	51.0 (32.9)[†]
Triglycerides, mmol/l	1.25 (0.7)	1.3 (0.8)	0.002	0.95 (0.5)[†]	1.03 (0.5)[†]
HDL cholesterol, mmol/l	1.49 (0.4)	1.53 (0.4)	<0.0001	1.78 (0.4)[†]	1.79 (0.4)[†]
Systolic blood pressure, mmHg	132.4 (14.4)	137.5 (18.4)	<0.0001	126.4 (15.2)[†]	128.1 (19.1)[†]

Supprimé : 17/11/05

Diastolic blood pressure, mmHg	81.3 (9.5)	82.9 (10.4)	<0.0001	77.2 (9.1)[†]	78.4 (9.8)[†]
Currently Smoke	25%	18%	<0.0001	13%[†]	12%[†]
IFG[§]	14%	16%	<0.0001	5%[†]	6%[†]
NCEP Metabolic Syndrome[‖]	10%	11%	<0.0001	6%[*]	8%[*]
Diabetes[#]	3.2%	6.1%	<0.0001	1.3%[†]	2.7%[†]
Taking Medication for:					
a. Diabetes[ψ]	1.5%	3.3%	<0.0001	0.6%*	1.5%*
b. Hypertension[ψ]	10%	18%	<0.0001	12%	19%
c. Dyslipidemia[ψ]	9%	19%	<0.0001	7%*	15%*

Data are presented as mean (SD) or %; reported p-values were calculated by t-tests and chi-square comparisons for proportions, respectively

*p < 0.05 between men and women at same exam; [†] p < 0.0001 between men and women at same exam

[‡] FPG=fasting plasma glucose,[§] IFG=FPG 6.10-6.99 mmol/L; ‖Metabolic syndrome, as defined by the National Cholest

[#] Treated with diabetes medication (oral hypoglycemic or insulin) or FPG ≥ 7.0 mmol/L

[ψ] Self-reported treatment with medication for these conditions at the time of the respective examinations

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Table 2. Adjusted means* for metabolic syndrome parameters by weight change groups after six years of
3,770 participants in the D.E.S.I.R. cohort by sex

PARAMETERS at D6 by sex	LOSS ≤ - 2 kg	STABLE 2 kg to + 2 kg	MILD GAIN + 3 to 5 kg	MEDIUM GAIN + 6 to 8 kg	LARGE GAIN ≥ + 9 kg
	n=404 (207 M; 197 F)	n=1786 (925 M; 861 F)	n=926 (433 M; 493 F)	n=395 (201 M; 194 F)	n=259 (104 M; 155
Waist girth, cm:					
Men	85.7 (0.3)	90.2 (0.1)	93.3 (0.2)	96.0 (0.3)	99.9 (0.4
Women	75.2 (0.4)	78.6 (0.2)	81.7 (0.2)	84.9 (0.4)	89.1 (0.4
Insulin, pmol/l:					
Men	40.0 (2.2)	52.0 (1.0)	59.0 (1.5)	70.7 (2.2)	91.2 (3.1
Women	38.3 (1.8)	46.1 (0.9)	55.0 (1.1)	60.7 (1.8)	69.1 (2.0
Glucose, mmol/L:					
Men	5.5 (0.05)	5.6 (0.02)	5.6 (0.04)	5.7 (0.05)	6.0 (0.07
Women	5.1 (0.04)	5.1 (0.02)	5.2 (0.03)	5.2 (0.04)	5.3 (0.05
HDL cholesterol, mmol/l:					
Men	1.63 (0.02)	1.56 (0.01)	1.50 (0.01)	1.46 (0.02)	1.40 (0.02
Women	1.89 (0.02)	1.83 (0.01)	1.76 (0.01)	1.70 (0.02)	1.69 (0.02
Triglycerides, mmol/l:					
Men	1.0 (0.04)	1.2 (0.02)	1.4 (0.03)	1.5 (0.05)	1.7 (0.06
Women	0.9 (0.03)	1.0 (0.01)	1.1 (0.02)	1.2 (0.03)	1.3 (0.03

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Systolic blood pressure,
mmHg:

Men	133 (1.1)	137 (0.5)	139 (0.7)	140 (1.1)	142 (1.5)
Women	125 (1.1)	127 (0.5)	129 (0.7)	130 (1.1)	132 (1.2)

Diastolic blood pressure,
mmHg:

Men	80 (0.7)	82 (0.3)	84 (0.5)	85 (0.7)	85 (0.9)
Women	77 (0.6)	78 (0.3)	79 (0.4)	80 (0.6)	81 (0.7)

*Data are presented as adjusted means (SE); Each model: D6 variable=D0variable+age+baseline weight+ weight change(

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