

Long-term studies of hemophilic arthropathy by Pettersson score – Evidences that joint damages in severe hemophiliacs occur since early years of life

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Introduction

Minimal or no treatments were given in the care of hemophiliacs in Taiwan before 1980s (Fig 1). The year 1984 was the most important turning point of year when the first hemophilia treatment center was established (at National Taiwan University Hospital, NTUH) and adequate treatments just began to be implemented. The influence of the difference in treatment on the development of hemophilic arthropathy in those patients we have seen through almost 30 years of care in two hemophilia treatment centers (at NTUH and CCH, Changhua Christian Hospital) will be evaluated.

Materials and Methods

Pettersson score was used to study the hemophilic arthropathy including ankles, knees and elbows in 107 cases of severe hemophiliacs during the year 1984 to 1986, 104 cases during 1997 to 2000 and 63 cases during 2007 to 2010. Mean joint score of a patient was the mean of the scores obtained from his 6 joints (Table 1 and Fig 2).

Statistical Methods

Multivariate analysis of the mean score by fitting multiple linear regression model with the stepwise variable selection method was used to see the effect of age on the change of joint score.

Results

1. In Table 2, the data revealed that:

- (1) For subjects born in the same calendar year, the mean score would increase at the rate of 0.1574 per year of age when the mean score was measured.
- (2) Yet, for subjects who were at the same age when their mean scores were measured, the subjects who were between 7 and 36.75 years old in 1984 had 0.8004 larger mean score than those who were less than 7 years old or older than 36.75 years old in 1984.

The two cut-off points for age in 1984, 7 and 36.75 years old, were empirically determined by fitting a multiple generalized additive model (GAM) with the smoothing technique applied to the effects of age at the measurement and age in 1984.

2. In Fig.3, nonparametric smoothing plot from GAM of mean score showed that:

- (1) If ages of patients in 1984 were > 0 i.e., they were born before 1984, they would receive minimal or no treatments. Their mean score increased when 0 to 7 years old but with milder severity (below “0” line of relative severity of predicted value of mean score), and steadily increased through 10 and up to 25 years old, slowed down till 36.75 years old, then went down.
- (2) For those born after 1984 (age in 1984 < 0), their mean scores were stable and much milder (below “0” line)

3. Multivariate analysis of the mean Pettersson joint score in patients who were born before and after 1979 (Table 3 and Fig 4.) and 1974 (Table 4 and Fig 5.) showed that the data were compatible with previous data and revealed that:

- (1) The mean scores increased with ages
- (2) Both cohort of patients who were born before and after 1979 but not 1974 showed statistical difference in mean score ($p=0.0037$ vs. $p=0.245$)

Discussions

1. In this regression analysis, we assumed that all 274 observations were independent. In fact, some of the subjects appeared in more than one cohort. They were repeatedly measured on their mean score at their different ages. Thus, some of the 274 observations were correlated. Yet, we could not identify them due to the loss of the detailed personal identification information.
2. Technically, violation of the independence assumption did not affect the estimates of the regression coefficients, but it would affect the estimates of the standard error of the estimates of the regression coefficient, and thus both the t test and p values in Table 3 were incorrect. However, since the p values were so small, we believed that the conclusion would still be correct even though the independence assumption was violated to some extent. Further studies are needed to verify the conclusion (Table 3 and Fig 4 ; Table 4 and Fig 5).
3. The subjects who were older than 36.75 years in 1984 would also suffer the harm due to the delay of the proper treatment available before 1984, but some of them might have worse conditions and thus died after 1984 so that the curve went down starting at the age of 25 years (the peak) in 1984 due to the selection bias.

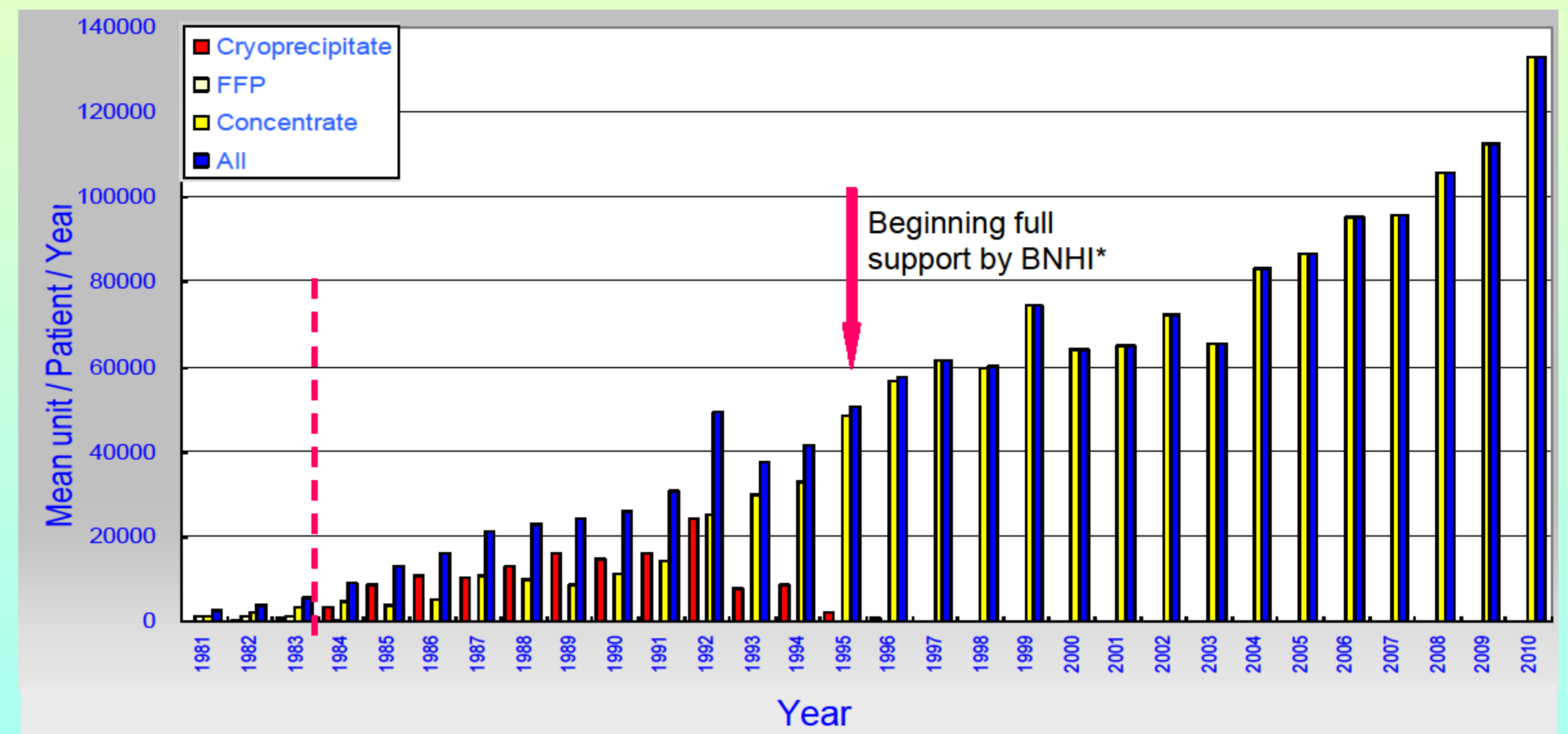


Fig. 1. Blood component therapy in severe hemophilia A at hemophilia treatment center of National Taiwan University Hospital

* BNHI: Bureau of National Health Insurance

Table 1. Three cohorts of severe hemophilic patients were measured for their mean Pettersson scores of three pairs of joints including ankles, knees and elbows, each at different time periods

Time period	1984-1986	1997-2000	2009-2010
No. of patients	107	104	63
Hemophilia A/B	96/11	84/20	49/14
Ages (years)			
Median*	22	24	28
Ranges	4-51	6-54	5-74
HTC**	NTUH**	NTUH	CCH**+NTUH

* Overall p -value = 0.01 by Kruskal-Wallis Test

** HTC: hemophilia treatment center

** NTUH: National Taiwan University Hospital (Northern part of Taiwan)

** CCH: Changhua Christian Hospital (Middle part of Taiwan)

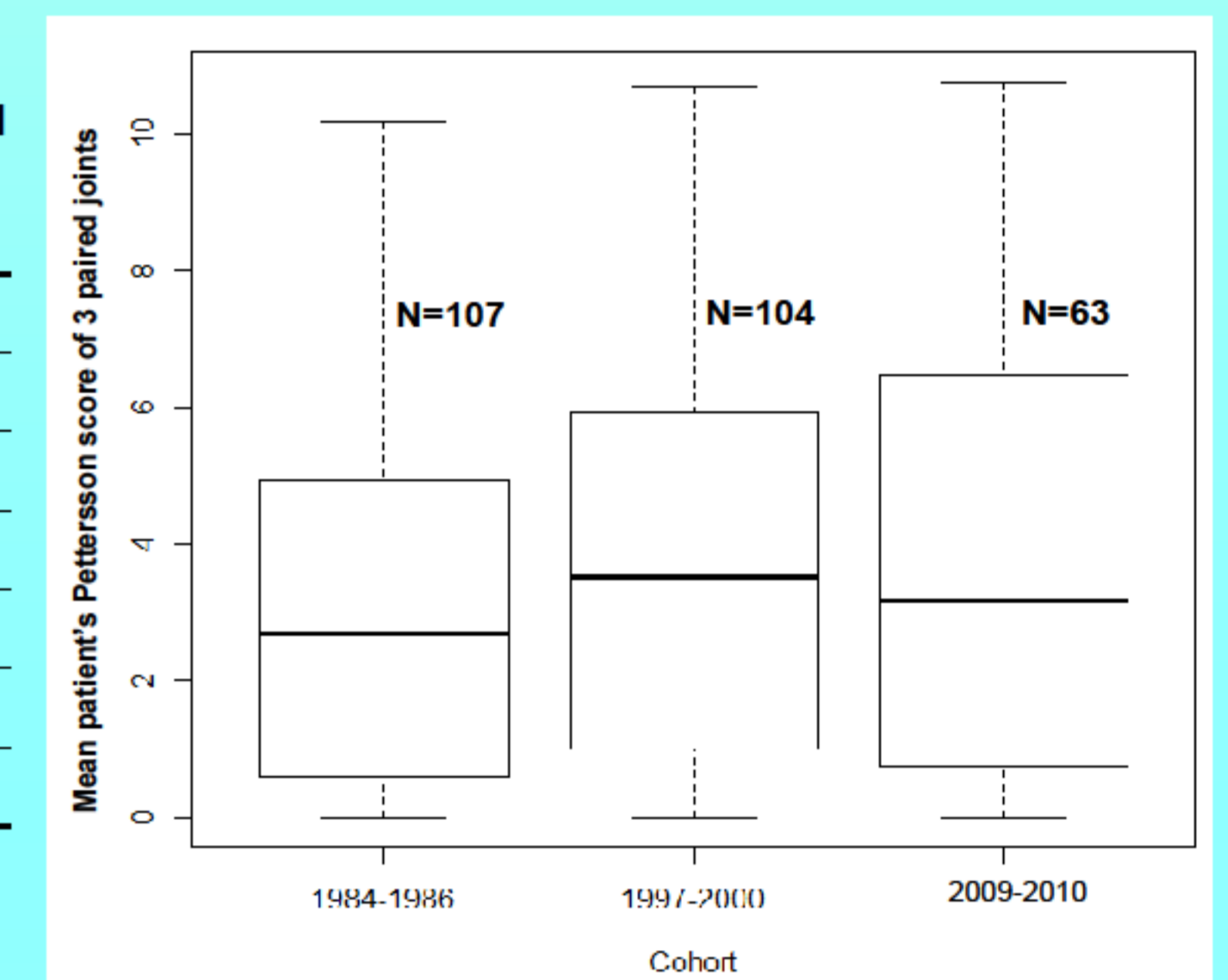


Fig 2. Distribution of mean patient's Pettersson score by intraquarter range and median value p -value = 0.2438 by Kruskal-Wallis rank sum test (Kruskal-Wallis chi-squared = 2.823, df = 2.)

Table 2. Multivariate analysis of the mean score by fitting multiple linear regression model with the stepwise variable selection method^a

Covariate	Regression coefficient	Standard error	t value	p value
Intercept	-0.8535	0.2715	-3.143	0.0019
Age (years)	0.1574	0.0103	15.268	< 0.0001
I(7 years < Age in 1984 < 36.75 years)	0.8004	0.2660	3.009	0.0029

^aMultiple linear regression model: $n=274$, $R^2 = 0.5468$, indicating a fair fit. The fitted regression equation is:

$$\text{Predicted value of mean score (Y)} = -0.8535 + 0.1574 \times \text{Age (year)} + 0.8004 \times I(7 \text{ years} < \text{Age in } 1984 < 36.75 \text{ years})$$

Where the "Age" (years) was the age of the subject when his mean score was measured and "I (condition)" was the indicator function, I (condition)=1 if the condition specified inside the parentheses was true, 0 otherwise.

Table 3. Multivariate analysis of the mean Pettersson joint score by fitting multiple linear regression model with the stepwise variable selection method in patients who were born before and after 1979

	Estimate	Std. Error	t value	p value
Intercept	-1.47	1.136	-1.29	0.199
Age	0.1574	0.0103	15.268	< 0.0001
I(7 years < Age in 1984 < 36.75 years)	0.8004	0.2660	3.009	0.0029

^aFor subjects born before 1979, the mean score would increase at the rate of 0.1590 per year of age.

^bFor subjects born after 1979, the mean score would increase at the rate of 0.1655 (= 0.1590 + 0.0055) per year of age.

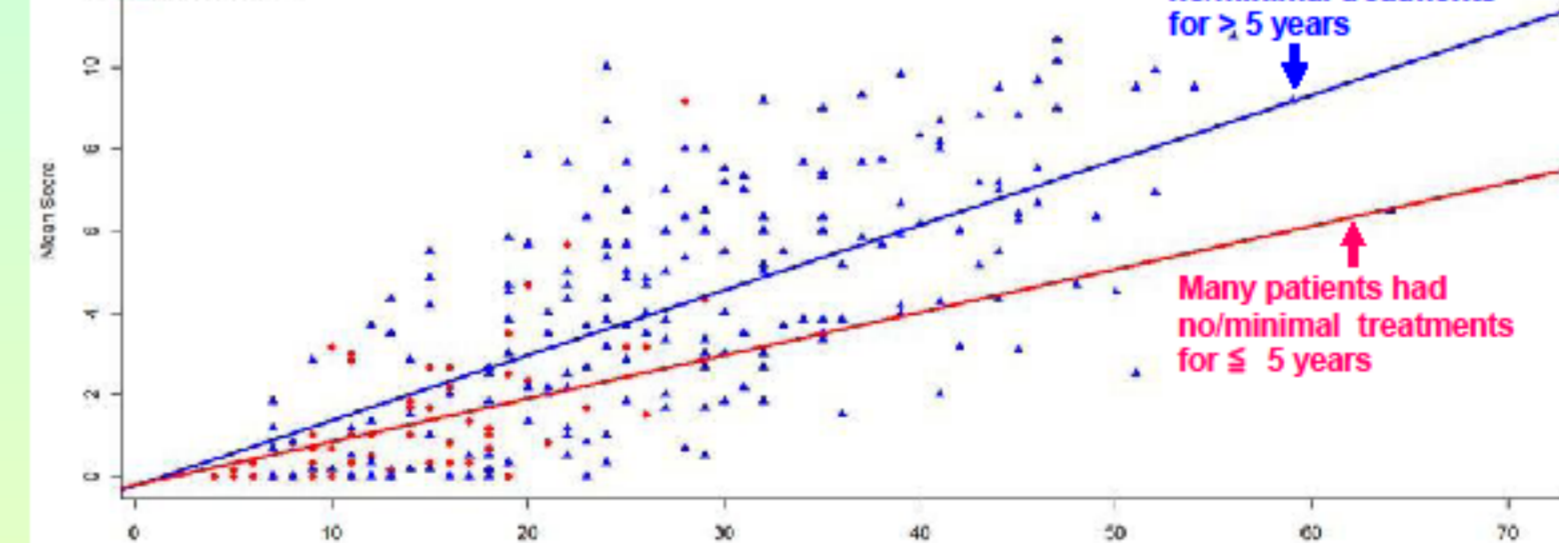


Fig 4. Scattered plot of mean joint score of the subjects born before and after 1979

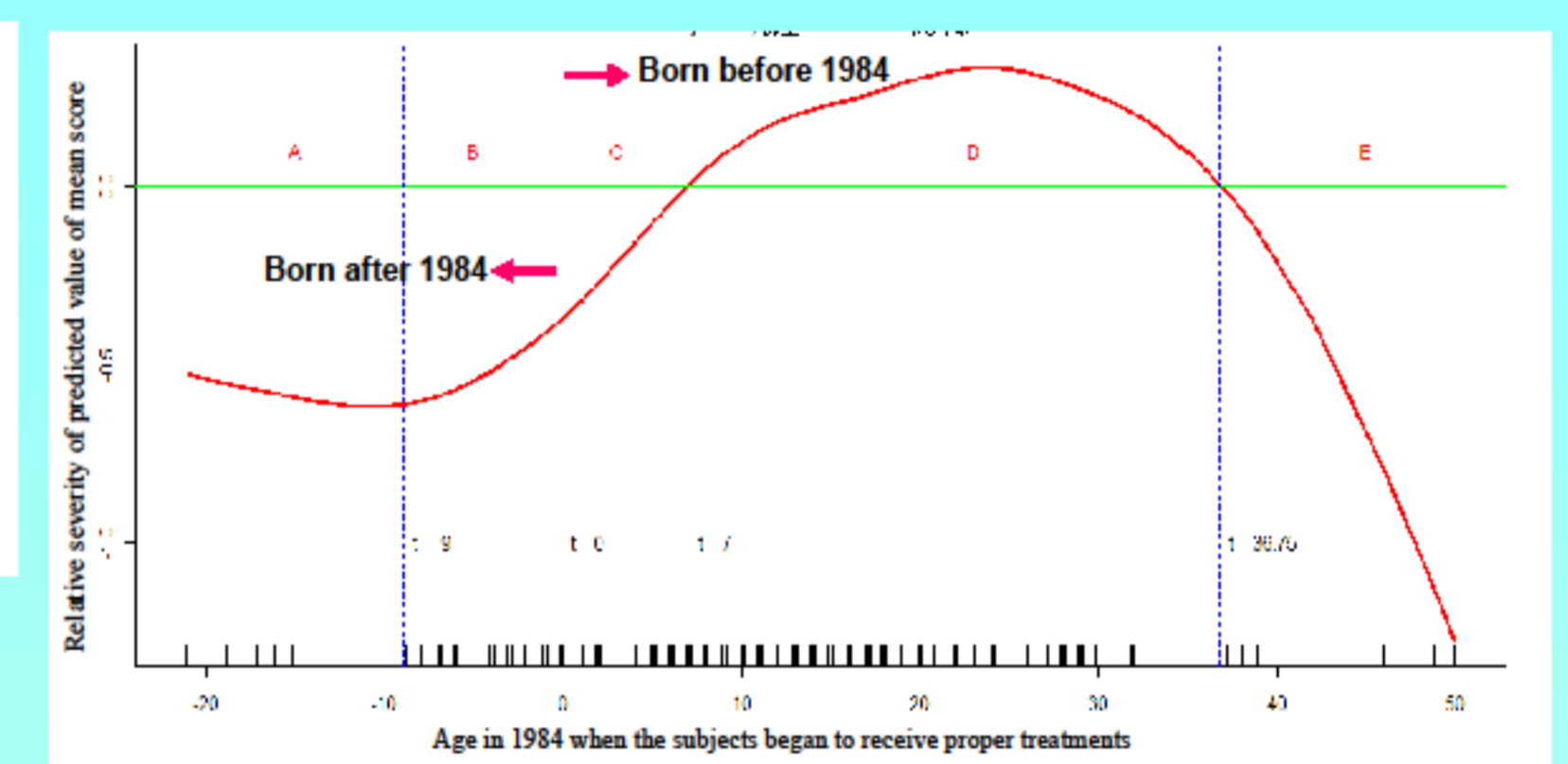


Fig 3. Nonparametric smoothing plot from GAM of mean score Adjusted by age at the measurement of mean score

Table 4. Multivariate analysis of the mean Pettersson joint score by fitting multiple linear regression model with the stepwise variable selection method in patients who were born before and after 1974

	Estimate	Std. Error	t value	p value
Intercept	-1.47	1.136	-1.29	0.199
Age	0.1574	0.0103	15.268	< 0.0001
I(7 years < Age in 1984 < 36.75 years)	0.8004	0.2660	3.009	0.0029

^aFor subjects born before 1974, the mean score would increase at the rate of 0.1662 per year of age.

^bFor subjects born after 1974, the mean score would increase at the rate of 0.1588 (= 0.1662 - 0.0054) per year of age.

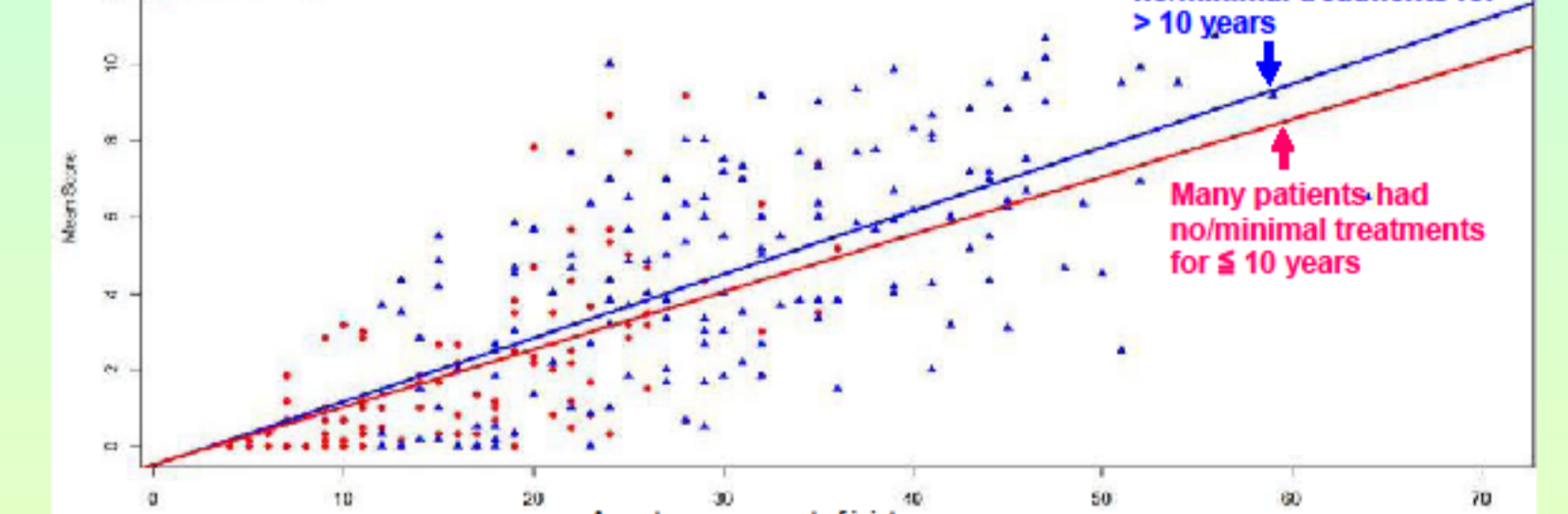


Fig 5. Scattered plot of mean joint score of the subjects born before and after 1974

Conclusions

1. In patients with severe hemophilia A and B who received no treatments or inadequate treatments, joint damages occurred in early year of life through 7 years old and most evident till 25 years old.
2. The mean joint Pettersson scores increased with ages indicated that no treatment and even on demand treatments could not prevent progressive damages of joint.
3. No treatment or inadequate treatments for up to 5 years since birth in severe hemophiliacs might not cause permanent damages of joint which could still be improved after on-demand treatments.
4. No treatment or inadequate treatment for 7 years or up to 10 years since birth in severe hemophiliacs would cause serious damages of joints which could not be improved significantly after on-demand treatments.

